ESTONIAN UNIVERSITY OF LIFE SCIENCES
Institute of Veterinary Medicine and Animal Sciences

Julia Eeva-Maria Sulonen

XYLITOL TOXICOSIS IN DOGS: CASE SERIES STUDY

KOERTE KSÜLITOOLIMÜRGISTUSE JUHTUMITE ANALÜÜS

Final Thesis
Curriculum in Veterinary Medicine

Supervisors: Assistant Kristel Peetsalu
Professor Toomas Orro

Tartu 2021

www.emu.ee
Eesti Maaülikool
Estonian University of Life Sciences

Estonian University of Life Sciences
Kreutzwaldi 1, 51014, Tartu Estonia

Abstract of Final Thesis

Author: Julia Eeva-Maria Sulonen

Curriculum: Veterinary Medicine

Title: Xylitol toxicosis in dogs: case series study

Pages: 59	Figures: 9	Tables: 13	Appendixes: 1

Chair: Chair of Clinical Veterinary Medicine

Field of research and (CERC S) code: 3. Health, 3.2. Veterinary Medicine

B750 Veterinary medicine, surgery, physiology, pathology, clinical studies

Supervisor(s): Kristel Peetsalu, Toomas Orro

Place and year: Tartu 2021

Xylitol is a five-carbon sugar alcohol widely used as artificial sweetener. Xylitol has a varied safety margin in mammals, from generally recognized as safe for humans to high toxicity in dogs. In dogs over 100 mg/kg is considered as a risk for hypoglycemia and over 500 mg/kg is considered as a risk for liver failure. Xylitol toxicity can be presented with two clinical syndromes, as hyperinsulinemia or as hepatic necrosis or combination of both. Some dogs might not develop clinical signs before the onset of liver failure. The increased popularity of xylitol has resulted in an increased trend in xylitol toxicosis in dogs. The aim of the thesis was to describe eight clinical cases of xylitol ingestion in dogs including clinical sings, associated laboratory values, treatment and outcome. The second aim was to compare this information from the case material to the literature. The case material was collected from a private small animal clinic in Finland covering years 2015-2019. The main differences to the recommended treatment protocol were: dextrose solution administration route was generally peroral instead of intravenous in the case material and duration of the initial treatment at the clinic was less than recommended 12-24 hours. No dog developed clinical signs of acute liver failure even though ingested xylitol dose exceeded both risk limits. The main finding in the laboratory values was that increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) enzyme activity were most common and consistent with the literature. Therefore, this thesis further supports ALT and AST liver cytosolic parameters being useful markers for the xylitol ingestion when ingested dose exceeds both risk limits.

Keywords: dog, xylitol, toxicosis, toxicity

www.emu.ee

Eesti Maaülikool

Estonian University of Life Sciences

Eesti Maaülikool Kreutzwaldi 1, 51014, Tartu		Lõputöö lühikokkuvõte	
Autor: Julia Eeva-Maria Sulonen		Õppekava: Veterinaarmeditsiin	
Pealkiri: Koerte ksülitoolimürgistuse juhtumite analüüs			
Lehekülgi: 59	Jooniseid: 9	Tabeleid: 13	Lisasid: 1
Õppetool: Kliinilise veterinaarmeditsiini õppetool ETIS-e teadusvaldkond ja CERC S-i kood: 3. Terviseuuringud, 3.2 veterinaarmeditsiin B750 Veterinaarmeditsiin, kirurgia, füsioloogia, patoloogia, kliinilised uuringud Juhendaja(d): Kristel Peetsalu, Toomas Orro Kaitsmiskoht ja -aasta: Tartu 2021			
Ksülitool on viie süsinikuguaatomiga suhkrualkohol, mida kasutatakse magusainena. Ksülitool on inimestele ohutu kuid koertele väga eluohtlik Koertel loetakse ksülitoosi doosi üle 100 mg/kg hüpoglükeemia riskiks ning üle 500 mg/kg maksakahjustuse riskiteguriks. Ksülitoolimürgistus esineb kahe kliinilise sündroomina: kas hüperinsulineemia või maksanekroosina; või need esinevad koos. Kliinilisi tunnuseid ei pruugi tekkida enne maksakahjustuse väljakujunemist. Ksülitooli suurenenud tarbimine ühiskonnas on kaasa toonud ksülitooli mürgistusjuhtude sagenemise koertel. Uuringu eesmärk oli kirjeldada kaheksat koerte ksülitoolisöömise haigusjuhtu. Kirjeldused hõlmavad kliinilisi tunnuseid, laboruuringute tulemusi, ravi ja paranemist. Haigusjuhtumeid võrreldi kirjandusandmetega. Andmed juhtumite kohta aastatel 2015–2019 koguti Soomes asuva väikeloomakliiniku andmebaasist. Erinevused soovitava ravijuhisega olid järgmised: dekstroosilahuse manustamine oli kliinikus pigem suukaudne kui veenisisene. Esmase ravi kestvus oli kliinikus lühem kui ravijuhises soovitatud 12–24 tundi. Kuigi tarbitud ksülitoolikogused ületasid riskipiire, ei kujunenud ühelgi koeral välja maksakahjustuse nähtavaid kliinilisi sümptomeid. Maksarakkude ensüümid ALT ja AST on olulised biomarkerid ksülitoolimürgistuse korral koertel, kui tarbitud doos ületab riskipiiri. Peamised laboranalüüside leiud olid kõrgenenud ensüümide alaniini aminotransferaas (ALT) ja aspartaadi aminotransferaas (AST) aktiivsuse tõus, mis vastab kirjanduse andmetele.			
Märksõnad: koer, ksülitool, toksikoos			

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACTH	adrenocorticotropic hormone
ALT	alanine aminotransferase
APCC	Animal Poison Control Center
aPTT	activated partial thromboplastin time
ASPCA	The American Society for the Prevention of Cruelty to Animals
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCS	body condition score
BW	body weight
CBC	complete blood count
DIC	disseminated intravascular coagulation
FDA	Food and Drug Administration
GGT	gamma glutamyl transferase
GRAS	generally recognized as safe
IM	intramuscular
IU	international unit
IV	intravenous
NAC	N-acetylcysteine
PO	*per os,* peroral
PT	prothrombin time
SAMe	S-adenosyl-L-methionine
SC	sub cutaneous
Xylon	wood or wood substance

INTRODUCTION

Xylitol is a five-carbon sugar alcohol. It is used as an artificial sweetener in many daily products such as chewing gums, toothpastes, pastilles, chewable vitamins and bakery products. The popularity of xylitol stems from its health benefits for humans and broad variety of usage possibilities.

Xylitol has a varied safety margin in mammals, from generally recognized as safe for humans to high toxicity in dogs. In dogs even as small amount as over 100 mg/kg is generally considered as a risk for hypoglycemia and 500 mg/kg is considered as a risk for liver failure (Dunayer, 2006). Increased use of xylitol in daily products has caused it to become a more common toxicant in dogs and there is a noticeable trend in its exposure (Cortinovis and Caloni, 2016).

Xylitol toxicosis in dogs occurs as two clinical syndromes: hyperinsulinemia or hepatic necrosis or as the combination of these two (Peterson, 2013). The most common clinical signs associated with xylitol toxicity are vomiting, lethargy, diarrhea, ataxia, seizures, restlessness and anorexia (Duhadway *et al.,* 2015).

The aim of the thesis was to describe eight clinical cases of xylitol ingestion in dogs including clinical sings, associated laboratory values, treatment and outcome. The second aim was to compare this information from the case material to the literature. The case material consisting of eight dogs was collected from a private small animal clinic in Finland covering years 2015-2019.

The first part of the thesis includes a literature review of xylitol toxicosis in dogs. This section collects xylitol usage properties, toxicokinetics, risk doses, clinical signs, associated laboratory values and treatment of xylitol toxicosis in dogs. The second part of the thesis consist of a case study of eight dogs that have ingested xylitol. This part discusses separately each case including the signalment and history, clinical signs, laboratory results, treatment and outcome. After all the individual cases, a summary of cases and descriptive statistics of the cases will follow. The

fifth chapter consists of discussion where the results from the case study are compared to the ones in the literature. The sixth chapter consist of conclusions of the study.

ACKNOWLEDGEMENTS

I would like to thank my supervisor Kristel Peetsalu for the guidance and support throughout the final thesis. I would like to also thank Professor Toomas Orro for contribution to my thesis.

I would like to thank my dear friend and colleague for making this case study possible. I would also like to thank my husband and family for all the support during my final thesis, journey of becoming a veterinarian and always.

1. LITERATURE REVIEW

1.1. Xylitol usages

Xylitol is a naturally occurring five-carbon sugar alcohol. It was first discovered by a German chemist Emil Fischer in late 19th century (Dunayer, 2006). The term xylitol originates from a Greek word *xylon* – that means wood or wood substance (Mäkinen, 2015). Xylitol can be produced from chemical hydrogenation of xylose or by alternative biotechnological processes (Ur-Rehman *et al.,* 2015). The United States Food and Drug Administration (FDA) declared xylitol as safe for human consumption in 1986 and xylitol was registered and generally recognized as safe (GRAS) (Janket *et al.,* 2019). Xylitol is also approved as a food additive in the European Union.

Xylitol is used as an artificial sweetener in many daily products such as in chewing gums, toothpastes, pastilles, chewable vitamins and bakery products. The popularity of xylitol stems from its health benefits for humans and broad variety of usage possibilities. Some of the health benefits of xylitol are its low glycemic index (Rahman *et al.,* 2014) and antimicrobial properties (Tapiainen *et al*., 2001). Therefore, xylitol is used in dental products and especially in chewing gums due to its anticariogenic properties (Ly *et al*., 2008). Especially in Finland xylitol is widely used in chewing gums or pastilles due to the dental health benefits. In Finland the recommended amount of xylitol consumption is five grams per day (Laitala and Pienihäkkinen, 2020). The recommendations are based on the research done on xylitol gum products on the prevention of dental caries in children and in adults. For example in the study of Newton *et al.* (2019) the consumption of xylitol gum was discovered to reduce caries increment by 33%. Whereas in the high-caries-risk adults consumption of xylitol gum 2.5 grams per day reduced significantly increment of initial and extensive caries lesions (Cocco *et al.,* 2017). Drinking water additives containing a hint of xylitol are available for oral health of cats and dogs. The increased use of xylitol products may expose dogs to xylitol products, for example Cortinovis and Caloni (2016) have discovered a noticeable trend in the exposure of dogs to xylitol containing products.

1.2. Toxicokinetics and mechanism of xylitol toxicity

The safety of xylitol varies among species and the oral LD50 of xylitol in mice is over 20 grams of xylitol per kilogram (Dunayer, 2006). Whereas consumption of xylitol in humans 130 g/day will cause diarrhea but no other abnormalities (Mäkinen, 2016; Murphy and Dunayer, 2018). Xylitol was not discovered to induce toxic effects in cats in the recent study of Jerzsele *et al.* (2018). In contrast to some other mammals, xylitol is a potent toxicant in dogs and can develop life-threatening clinical signs and even death.

Xylitol is an intermediary product of carbohydrate metabolism both in humans and animals (Ur-Rehman *et al.,* 2015). The absorption of xylitol is different among species, for example in people and rats the absorption is slow and in dogs the absorption from gastrointestinal tract is rapid and almost complete (Dunayer, 2006). The most of the xylitol metabolism occurs in the liver by oxidation to D-xylose (Duhadway *et al.,* 2015). D-xylose is then phosphorylated to D-xylose-5-phosphate, which is an intermediate of pentose phosphate pathway (Duhadway *et al.,* 2015). D-xylose-5-phosphate is later converted into glyceraldehyde-6-phosphate or fructose-6-phosphate and finally forming glucose, glycogen or lactate (WHO, 1977) but the majority of xylitol is still converted into glucose (Duhadway *et al.,* 2015). The remaining 20-30% of ingested xylitol can be metabolized extrahepatically in kidneys, lungs, erythrocytes, fat stores and myocardium where it is converted into carbon dioxide and water through carbohydrate metabolism (Wang and van Eys 1981; Schmid and Hovda, 2016).

In dogs ingestion of xylitol results in dose dependent increase in plasma insulin concentration (Duhadway *et al*., 2015). The mechanism of xylitol induced hyperinsulinemia has been demonstrated. In a study of anesthetized dogs indicated that xylitol intrinsically stimulates insulin secretion by pancreatic islet β cells rather than its metabolites (Xia *et al.,* 2009). Whereas insulin release from pancreas can lead to commonly associated hypoglycemia because insulin is released 2.5-7 times more by xylitol than by glucose (Duhadway *et al.,* 2015). As a result, blood glucose starts to decrease, and hypoglycemia commonly develops.

In addition to the insulin surge xylitol has also been associated with the possibility of hepatic injury but the mechanisms are not clear yet (Peterson, 2013). Based on the studies of Zhang *et al*. (2015) the consideration was that xylitol is not a direct hepatotoxicant and its toxicity is

related to a more complex pathophysiological process. One possible mechanism is that phosphorylated intermediates from hepatic metabolism of xylitol can deplete adenosine triphosphate (ATP) in liver and without adequate ATP values cellular function is inadequate and cellular necrosis might result (Woods and Krebs, 1965; Dunayer and Gwaltney-Brant, 2006). The other possible mechanism is considered to be a result of reactive oxygen species. Xylitol metabolism produces high concentration of cellular nicotinamide adenine dinucleotide and hence mitochondrial metabolism of these can produce reactive oxygen species which are able to damage cellular membranes and decrease hepatocyte functions (Dunayer and Gwaltney-Brant, 2006).

1.3. Doses

The owners of dogs may not always know which xylitol products their dogs have ingested or especially the amount of the xylitol. Nevertheless, the amount of xylitol should be evaluated, therefore the literature recommendations for dose calculations can be essential. If xylitol is the first sugar alcohol listed in the ingredient list the dose should be based on the total amount of sugar alcohols per piece of gum and if xylitol is not the first sugar alcohol listed then it should be assumed that each piece contains 300 mg of xylitol (Dunayer, 2006). The Finnish webpage called xylitol.net contains information about the most common xylitol products in the Finnish market. On the website one can find accurate information on how much xylitol these common xylitol products contain. This can be useful when evaluating the ingested dose of xylitol.

For dogs the xylitol toxicity is high even at small oral doses, the dogs who have ingested xylitol over 100 mg/kg are at risk for developing hypoglycemia and the lowest estimated dose resulting in liver failure is over 500 mg/kg (Dunayer, 2006). Even smaller xylitol doses can result in hypoglycemia as this was the case in the study by Duhadway *et al.* (2015) where a dog was estimated to have ingested a dose of 30 mg/kg. Based on the reports of Animal Poison Control Center (APCC) of the American Association for the Prevention of Cruelty to Animals (ASPCA) mild clinical signs are expected with doses 100 mg/kg but when a dog has ingested more than 50 mg/kg it should at least justify decontamination and blood glucose monitoring (Murphy and Dunayer, 2018). In the study of Xia *et al.* (2009) the oral dose of 4,000 mg/kg did not cause mortality but induced clinical signs. A successful management of a dog that had ingested a dose

as high as 45,000 mg/kg has been carried out (Schmid and Hovda, 2016). The dog had clinical signs of hypoglycemia, hepatic failure and coagulopathy.

The amount of xylitol ingested varies a lot among individual cases and in the study of Duhadway *et al*. (2015) 192 client owned dogs were evaluated retrospectively with known or suspected xylitol ingestion. The median quantity of ingested xylitol gum was ten pieces with the median estimated dose of 320 mg/kg (Duhadway *et al.,* 2015). The same study discovered that there was no association between the estimated dose ingested and initial and lowest blood glucose in the population in dogs that became hypoglycemic (Duhadway *et al.,* 2015).

It is contradictory that xylitol is considered as a potent toxicant for dogs when drinking water additives containing xylitol are available for dental health for dogs and cats. In a pilot study of xylitol-based drinking water additive in dogs the amount of xylitol in the final product if prepared as package instructions was 0.05 mg/ml and with daily water intake of 60 ml/kg of body weight for example a dog weighting 15 kg would get a total xylitol dose of 45 mg (Lowe and Anthony, 2020). This dose is still under the dose usually causing clinical signs (100 mg/kg) but the potent toxicity of long lasting administration of low xylitol dosages is unknown (Lowe and Anthony, 2020).

1.4. Clinical signs and laboratory value changes

Xylitol toxicity can be presented as two clinical syndromes with associated clinical signs, such as hyperinsulinemia or as hepatic necrosis or combination of both (Peterson, 2013). The dog can be presented without any clinical signs or have typical clinical signs of xylitol toxicosis. Duhadway *et al*. (2015) evaluated retrospectively 192 dogs with known or suspected xylitol ingestion and the most common clinical signs of xylitol toxicosis were from highest to lowest: vomiting, lethargy, diarrhea, ataxia, seizures, restlessness and anorexia. APCC database had similar results as the most common clinical signs reported were vomiting, lethargy and weakness (Murphy and Dunayer, 2018). When lethargy and weakness occurred dogs were generally hypoglycemic on presentation (Murphy and Dunayer, 2018).

Xylitol is rapidly absorbed after ingestion and this can result in peak plasma levels at 30 minutes after ingestion (Murphy and Dunayer, 2018). Vomiting is usually the first clinical sign of xylitol toxicosis (Dunayer, 2006). Hypoglycemia might develop 30-60 minutes after the ingestion but can be delayed up to 12 hours (Dunayer 2004; 2006). This delay might be associated with the formulation of the product and the amount of mastication (Murphy and Dunayer, 2018). Seizures can already occur in 30-40 minutes after ingestion (Peterson, 2013).

In the study of Xia *et al.* (2009) dogs were orally dosed 1,000-4,000 mg of xylitol/kg and were reported to show sharp increase of plasma insulin concentration within 20 minutes with peak at 40 minutes after ingestion. The dogs glucose levels began to decrease 30 minutes after xylitol dose and were the lowest at 50-60 minutes after ingestion and the blood glucose concentrations increased to similar concentrations at 90 minutes as in the control group (Xia *et al.,* 2009).

Insulin is known to shift potassium and phosphorus into intracellular space therefore during xylitol toxicosis in dogs hypokalemia and hypophosphatemia can occur. According to APCC database some dogs developed mild-to-moderate hypokalemia or hypophosphatemia within 12 hours after the ingestion of a xylitol product (Murphy and Dunayer, 2018). Hyperphosphatemia may occur in some dogs and may indicate a poorer prognosis as in the case study of Dunayer and Gwaltney-Brant (2006). In the study four of five dogs that died or were euthanized due to xylitol toxicosis had hyperphosphatemia (Dunayer and Gwaltney-Brant, 2006). Hyperphosphatemia may be due to decreased hepatic regeneration or phosphate release from liver necrosis (Shakil, 2005). Hyperphosphatemia was also detected in the retrospective study of Duhadway *et al.* (2015). In the study of Duhadway *et al.* (2015) six of seven dogs that were hyperphosphatemic were 12 months of age or less. Therefore, hyperphosphatemia can also be due to developing bones (Nelson, 2012). Whereas hypoglycemia can have an effect on erythrocyte membranes integrity resulting in release of bilirubin (Peterson, 2013). In the study of Xia *et al.* (2019) plasma gamma glutamyl transferase (GGT) and direct bilirubin were unchanged in the study suggesting that hepatic damage was not associated with effects on the biliary system. Increased plasma total bilirubin was reported represented increased indirect bilirubin which was presumably due to hemolysis (Xia *et al.,* 2009). APCC has reports of some dogs with high serum activities of liver enzymes have developed hyperbilirubinemia and coagulopathies suggestive of acute hepatic necrosis (Dunayer and Gwaltney-Brant, 2006).

Hyperglycemia has also been reported and may be similar to Somogyi phenomenon that occurs with insulin overdoses (Dunayer, 2006). In Somogyi phenomenon hypoglycemia or rapid decline of blood glucose induces release of counterregulatory hormones such as glucagon, epinephrine, cortisol and growth hormone and leads to rebound hyperglycemia (Fracassi, 2017). Counter regulation occurs when blood glucose is less than 3.6 mmol/l or glucose concentration drops rapidly within two to three hours (Fracassi, 2017).

As xylitol toxicosis may be presented as either of the two clinical syndromes or as the combination of them, hepatopathy can develop one to two hours post ingestion but delayed onset is also possible with 9-72 hours post ingestion (Peterson, 2013). According to APCC database the time limit to detect liver enzyme elevations varied from four hours to 24 hours, but in some cases alanine aminotransferase (ALT) elevated in less than four hours (Murphy and Dunayer, 2018). In acute hepatic failure lethargy, icterus, vomiting, petechiae, ecchymoses and gastrointestinal hemorrhages may develop (Peterson, 2013). Coagulopathy is a common finding in acute hepatic failure and results from combination of impaired production of clotting factors as a result of acute loss of majority of hepatic mass and disseminated intravascular coagulation (DIC) may be associated with severe hepatic necrosis (Dunayer and Gwaltney-Brant, 2006). ASPCA APCC reports show that some of the dogs developed elevated liver enzyme activity within 12-24 hours after ingestion of xylitol and several of these dogs developed acute liver failure (Dunayer, 2006). Some dogs might not develop hypoglycemia before sings of acute hepatic failure that occurred in APCC reported dogs in 9-72 hours post ingestion (Dunayer and Gwaltney-Brant, 2006). Clinicopathologic changes with dogs that developed acute hepatic failure and coagulopathy included marked increase in serum ALT activity, mild to moderately increase in serum alkaline phosphatase activity, moderate to severe hypoglycemia, mild to moderate hyperbilirubinemia, moderate to marked prolongation of clotting times, mild to moderate thrombocytopenia and mild to moderate hyperphosphatemia (Dunayer and Gwaltney-Brant, 2006).

1.5. Treatment

Based on the reports of APCC when a dog has ingested more than 100 mg/kg xylitol it is at risk of developing hypoglycemia and when a dog has ingested more than 500 mg/kg it is at risk of

liver failure (Dunayer, 2006). There is no exact knowledge on whether the reason for liver failure is dose related or idiosyncratic (Dunayer, 2006). Only mild clinical signs due to hypoglycemia are expected when a dog has ingested less than 100 mg/kg but when the dose is as small as over 50 mg/kg the dog should be taken to a clinic at least for decontamination and blood glucose monitoring (Murphy and Dunayer, 2018). When ingestion of xylitol is suspected the owner can rub corn syrup, honey, glucose syrup or 50% dextrose on tissues of the mouth and lining of the cheek of the dog and later administer per orally when the patient is able to swallow (Idowu and Heading, 2018). However studies have shown limited buccal absorption and hence these methods are relatively ineffective unless the dog is able to swallow the syrups (Gonzalez and Silverstein, 2019).

When a patient arrives to the clinic the baseline blood glucose should be measured. Other initial blood work on presentation should include electrolytes, blood glucose, baseline liver profile, baseline complete blood count and serum phosphorus. Emesis should be induced only in those patients who have not vomited prior and no contraindications are present. Induction of emesis is not recommended if the patient has ingested 100% xylitol products more than 30 minutes ago because of possibility for rapidly developing clinical signs of hypoglycemia due to this form of product (Murphy and Dunayer, 2018). The time limit for effective decontamination by emesis induction can be narrow due to rapid absorption of xylitol. Xylitol can be absorbed already in 30 minutes (Murphy and Dunayer, 2018). Therefore decontamination should be done as early as possible. Induction of emesis can be generated via apomorphine for example 0.04 mg/kg intramuscularly (IM) (Plumb, 2018) or by ropinirole eye drops (Suokko *et al.,* 2020). It should be taken into account that emetics usually do not remove more than 80% of the material in the stomach, more likely 40-60% and even after successful induction of emesis appropriate treatment should be continued (Plumb, 2018).

Antiemetics should be given to those patients who have already vomited by self-induced or with emesis-inducing medications enough for decontamination of xylitol. Maropitant 1 mg/kg subcutaneously (SC) or intravenously (IV) or Metoclopramide 0.2-0.5 mg/kg perorally (PO), SC, IM or IV can be used for antiemetic treatment (Plumb, 2018). Maropitant negates the emetic effects of apomorphine whereas metoclopramide may negate the emetic effects (Plumb, 2018). Gastroprotectants can also be considered for treatment. Activated charcoal is not recommended due to poor binding in vitro studies and being also pH dependent (Cope, 2004).

Electrolyte laboratory measurement can be repeated in 8-12 hours after exposure with focus on possible hypokalemia that should be treated whereas once daily phosphorus evaluation should be sufficient (Murphy and Dunayer, 2018). Blood glucose should be evaluated at least every two hours or even more often if patient is severely affected for the first 12 hours but evaluation may be needed for longer than 12 hours if hypoglycemia persist (Murphy and Dunayer, 2018). Whereas according to Peterson (2013) blood glucose values should be obtained in addition to initial measurement 30 minutes after the initial measurement, 60 minutes after the initial measurement and then hourly for the next 12 hours. Liver enzymes should be re-evaluated in 12, 24 and 48 hours later and if elevation occurs coagulation parameters should be monitored and complete blood count (CBC) to evaluate possible thrombocytopenia (Murphy and Dunayer, 2018). In contrast to recent case report, Dunayer and Gwaltney-Brant (2006) recommended the evaluation of liver enzymes, total bilirubin concentration, platelet counts and coagulation parameters to be monitored for 48 to 72 hours or longer.

Hypoglycemia is defined as a blood glucose concentration of <3.3 mmol/l. If hypoglycemia is present, intravenous dextrose solution 25% 1-2 ml/kg bolus should be administered followed by intravenous fluids containing 2.5-5% dextrose (Murphy and Dunayer, 2018). It is emphasized that dextrose concentrations greater than 5-7% should be administered via a central line because phlebitis due to high tonicity can occur otherwise (Gonzalez and Silverstein, 2019). Hence dextrose bolus can be administered for example as 5% dextrose crystalloid solution 3-6 ml/kg intravenous bolus to peripheral vein. Dextrose can prevent hypoglycemia in mild toxicosis and may be hepatoprotective (Murphy and Dunayer, 2018). The treatment with dextrose is recommended to start immediately whether or not hypoglycemia is present when ingested xylitol dose is >500 mg/kg (Dunayer, 2006).

Liver protectants and antioxidants are recommended by many authors even though their effects on xylitol toxicosis have not been established. N-acetylcysteine (NAC), S-adenosyl-L-methionine (SAMe), Silymarin or vitamin E may be used (Dunayer, 2006). Glutathione is tripeptide synthesized from L-glutamate, L-cysteine and glycine and its essential antioxidant stored mainly in hepatocytes (Lidbury, 2017). Reduced hepatic concentrations of glutathione have been observed in for example in necroinflammatory liver disease in cats and dogs and also

in cats with hepatic lipidosis hence oxidative injury has a great role in different hepatobiliary disease (Lidbury, 2017).

SAMe has a central role in glutathione synthesis therefore it may help to prevent oxidative injury (Lidbury, 2017). Recommended dose for SAMe is 20 mg/kg PO once daily to an empty stomach (Plumb, 2018). NAC is formulation of L-cysteine used to refill hepatic intracellular cysteine and glutathione protecting against oxidative damage (Lidbury, 2017). Intravenous administration of NAC is recommended in serious toxicosis and in uncontrolled vomiting. Recommended initial dose for NAC is 140-180 mg/kg IV (diluted to 5% with saline and given slowly over 15-20 minutes) or 280 mg/kg PO. Followed by 70 mg/kg PO or IV every six hours for minimum of seven treatments so with large overdoses it may be needed up to 17 treatments (Plumb, 2018).

Silymarin has inhibiting effects on lipid peroxidase and beta-glucuronidase and it acts as anti-oxidant and free radical scavenger, can prevent toxin penetration into hepatocytes and increase glutathione content in liver (Plumb, 2018). Silybin is the most bioactive isomer of silymarin but no consensus exists for dose in veterinary and human patients. One recommended dosage for dogs is 20-50 mg/kg PO once daily (Plumb, 2018).

Vitamin E supplements have been previously recommended for hepatobiliary diseases but there is no scientific data (Plumb, 2018). E-vitamin is antioxidant and scavenging free radicals. The recommended dose of most biologically active form of vitamin E, alpha-tocopherol for dogs is 10-15 IU/kg PO once daily (Lidbury, 2017). Also 100-400 IU PO twice daily of E-vitamin is recommended for dogs (Dunayer, 2006). Silybin and e-vitamin are added in some veterinary labeled SAMe products so separate administration may not be needed or at least total amounts should be calculated.

If hepatic damage leading to prolonged coagulation occurs, vitamin k1 therapy is recommended and plasma transfusions considered (Murphy and Dunayer, 2018). Hospitalization should in total last at least 12-24 hours after ingestion due to the risk of delayed-onset of hypoglycemia (Murphy and Dunayer, 2018). In addition, patients should receive frequent feeding until blood glucose level has been stabilized. At home frequent feeding is important. Adding dietary fiber to the diet may assist the elimination of possible wrapper materials (Murphy and Dunayer,

2018). Hepatoprotective medications should be continued as previously described, for example at least SAMe or NAC.

Prognosis is good when induction of vomiting is generated early with effective management of hypoglycemia even in cases with mild liver enzyme elevations. Prognosis is more guarded when episodes of profound hypoglycemia or significant liver enzyme elevations occur, suggesting hepatic necrosis (Murphy and Dunayer, 2018). Guarded to poor prognosis is with fulminant hepatic failure (Peterson, 2013).

If owner is not certain whether the dog has ingested xylitol differential diagnosis should be considered for hypoglycemia and hepatopathy. Differentials for hypoglycemia can include insulinoma, insulin overdose, hypoadrenocorticism, starvation, hunting dog hypoglycemia, juvenile hypoglycemia and hepatic disease. Differentials for hepatopathy can include infection, *Amanita* mushrooms, blue-green algae, acetaminophen, aflatoxins and other hepatotoxic agents (Peterson, 2013).

2. AIMS OF THE STUDY

The aim of the thesis was to describe eight clinical cases of xylitol ingestion in dogs including clinical sings, associated laboratory value changes, treatment and outcome. The second aim was to compare this information from the case material to the literature. The eight dogs visited a private small animal clinic in Finland during years 2015-2019. The case material was collected retrospectively from the clinic database.

3. MATERIALS AND METHODS

Cases were retrospectively selected by reviewing clinical records from a patient database KliniQ (Terakuu Oy., Keuruu, Finland) of a private small animal clinic located in Finland. Clinical records from 2015-2019 including term xylitol were chosen as case population with result of 17 cases. Some cases contained other toxications in addition to xylitol and they were left out from the final case material. The final case sample consisted of eight dogs that were chosen according to the most complete information and diagnosis of xylitol ingestion.

All patient owners were contacted by email and asked for their consent to take part in this research. All data was handled anonymously. The data collected from the patient database included patient's signalment, brief medical history, history including the name of the xylitol product if known and estimated quantity ingested, clinical signs reported by owner, clinical examination, laboratory results, diagnosis, treatment at clinic, treatment guidance for home and control visits if patient came to the same clinic for control visit.

The signalment included patients' age in years, sex (female/male) and body weight (kg). The brief medical history of previously diagnosed ongoing diseases, allergies and current medications were reported. History included xylitol ingestion. If there were more data the history also included possible amount of ingested xylitol and estimated time when it had occurred. Some owners knew the xylitol product (for example 100% xylitol) gum/pastilles. History included if the owner of the patient had recognised associated clinical signs before arriving to clinic.

Clinical examination included body condition score (BCS) of one to five with score three being ideal, mentation, mucous membrane color, moisturity of mucous membranes, capillary refill time, auscultutation, heart rate/rhythm, femoral pulse synchronicity, metatarsal pulse quality, breathing type, respiratory sounds, palpation of abdomen and lymph nodes. In some of the dogs the rectal temperature was also saved to database.

The complete blood count was determined by commercial fluorescent laser flow cytometry method (IDEXX Procyte Dx Hematology Analyzer, IDEXX Laboratories, Inc, Westbrook, Maine). The blood biochemistry, electrolytes and phosphorus was measured by commerically available IDEXX dry chemistry slides (Chem 10, Chem 17, Lyte 4) with commercial in clinic analyzer (IDEXX Catalyst One Analyzer, IDEXX Laboratories, Inc., Westbrook, Maine). The insulin metabolism was determined by commercially available in clinic immunoassay analyzer (AIA- 360 Automated Immunoassay Analyzer, Tosoh Bioscience, Inc., South San Fransisco, CA, U.S.A). In some dogs the blood gases were measured by in clinic commercial blood gas and electrolyte analyzer (IDEXX VetStat Electrolyte and Blood Gas Analyzer, IDEXX Laboratories, Inc., Westbrook, Maine) and coagulation parameters were also evaluated in these dogs by commercial capillary driven micro fluidic technology analyzer (QuickVet analyzer, Zoetis Denmark, Aps., Farum, Denmark). In one dog adrenal gland panel was measured by commercially available in clinic immunoassay analyzer (AIA- 360 Automated Immunoassay Analyzer, Tosoh Bioscience, Inc., South San Fransisco, CA, U.S.A).

The compared laboratory values in the study were insulin, glucose, potassium, phosphorus, total bilirubin, aspartate aminotransferase (AST), ALT, prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombocytes. If the dog was brought to the same veterinary clinic for the control visit these laboratory values were included in the case study.

The ingested amount of xylitol was evaluated by two different methods. The method one was to evaluate as recommended in the literature when xylitol is mentioned as the first sugar alcohol in the ingredient list of xylitol product. The xylitol amount was estimated by calculating the total amounts of sugar alcohols per piece of xylitol gum. When the exact xylitol product was not known, the product used for calculations was Jenkki Xylitol gum containing 68% xylitol. It was used for the dog number three, five and eight. The dog number one had eaten 30 grams of pure xylitol pastilles with content of 95% xylitol and dog number seven had eaten half from the Läkerol pastil package with estimated ingested amount of 18 grams with 50% of xylitol content.

The second method was to evaluate the ingested amount of xylitol so that each piece contains one gram of xylitol as had been done previously in the retrospective study of Duhadway et *al*. (2015). In both methods each gum was evaluated to weight 1.3 grams (xylitol.net). In addition,

the pastilles were assumed to weight 1.3 grams. When the exact size of the xylitol gum package was not known the used size was 80 grams in the estimations. The owners were not aware of the amount of xylitol ingested by dog number four and six, so the ingested amount of xylitol was not evaluated in these dogs.

4. RESULTS

4.1.Dog 1

Signalment and history: A seven-year-old male dog weighting 22.4 kg was evaluated at the veterinary clinic due to shivering and weakness after ingestion of xylitol pastilles. Approximately one hour prior to presentation, the dog had ingested 30 grams of pastilles containing 95% xylitol. The ingested dose was approximately 1,030 mg/kg (method two) to 1,272 mg/kg (method one) hence exceeding both risk limits. The dog had no previously diagnosed significant diseases or allergies. There were no ongoing medications.

Clinical examination: The behavior and mentation of the dog were fairly alert and it was able to walk. The BCS of the dog was 2.5/5 with normal muscle mass. The mucous membranes were light pink and moist with capillary refill time within reference range. The heart rate was 120 beats/min. Heartbeat synchronized with femoral pulse and metatarsal pulse was moderate. The breathing type was costoabdominal and without hearable abnormalities in breathing sounds. Sings of abdominal pain were not elicited. No abnormalities were detected in superficial lymph node palpation.

Laboratory results: The initial diagnostics included biochemistry panel (Chem 10), AST, electrolytes, insulin metabolism, lactate and blood coagulation parameters. The serum insulin concentration was slightly increased from the reference (Table 1). The plasma ALT enzyme concentration was slightly increased and AST was almost four times over the reference value (Table 1). The dog had mild hypoglycemia and mild hypokalemia (Table 1). The dog had moderate hyperlactatemia as lactate was 4.33 mmol/l. The blood coagulation parameters (PT, aPTT) were within reference limits (Table 1). Other measured values were within reference limits.

Table 1. Laboratory findings dog 1

Parameter	Reference range	Time from the initial test
		0 h
Insulin µIU/ml	8-32	35.8
Glucose mmol/l	4.11-7.95	2.90
Potassium mmol/l	3.5-5.8	3.4
AST U/l	0-50	190
ALT U/l	10-125	173
PT s	14-19	17.8
aPTT s	75-105	98

Note. AST – aspartate aminotransferase, ALT – alanine aminotransferase, PT – prothrombin time, aPTT – activated partial thromboplastin time.

Treatment: Therapy included the induction of vomiting with apomorphine, maropitant for antiemetic treatment. The vomitus contained food and some xylitol pastilles. Intravenous Lactated ringer's solution bolus was administered followed by constant rate infusion for two and a half hours. The dog was fed once per hour with tryptophan and dextrose. Vitamin B was administered IM. The dog was discharged on the same day with NAC first dose of 232 mg/kg followed by 58 mg/kg PO every eight hours for six to 12 times. Feeding was advised to be given every two hours for the next 24 hours. Control visit was recommended in 24-48 hours. The owner didn't bring the dog to the control visit at least no to the same clinic.

4.2.Dog 2

Signalment and history: A three-year-old female dog weighting 35.0 kg was evaluated at the veterinary clinic due to ingestion half of a gum bag containing 64% xylitol. The exact size of the gum bag was not known hence the used estimation size for dose calculations was 80 grams. The estimated ingested amount of xylitol was 731 mg/kg (method one) to 879 mg/kg (method two) exceeding both risk limits. The general wellbeing of the dog had deteriorated in the car on the way to the clinic. The dog also had urinated on itself. The dog had no previously diagnosed significant diseases or allergies. The dog had been bred three weeks ago.

Clinical examination: The mental status of the dog was poor and not reacting. Its pupils were miotic and not reacting to light. The palpebral and menace reflexes were normal. The dog had

otherwise weakened cranial reflexes with mandible and the tongue being relaxed. The mucous membranes were light pink and moist, capillary refill time within reference limits. The dog's heart rate was 60 beats/min. The heartbeat synchronized with femoral pulse and metatarsal pulse was moderate. The breathing rhythm and type was normal, no abnormalities were detected in auscultation of the breathing sounds. The rectal temperature was 38.9°C. The body condition score was evaluated to be 3/5 with good muscle mass.

Laboratory results: Initial diagnostics included plasma biochemistry (Chem 17), CBC, blood coagulation parameters, adrenal gland panel, insulin metabolism, instant glucose and blood gases were analyzed. The serum insulin concentration was markedly increased (Table 2). Coagulation parameters were within reference values (Table 2). Cortisol and adrenocorticotropic hormone (ACTH) were markedly increased as cortisol was 345.0 nmol/l (reference 14-180 nmol/l) and ACTH was 968.9 pg/ml (reference 6-58 pg/ml). CBC was within reference limits. The results from venous blood gas analysis revealed that patient had metabolic acidosis as pH was 6.95, pCO2 was within reference without compensation and bicarbonate was low 9.2 mmol/l (Table 3). There were not results from potassium and this can be due to extremely low values or a laboratory error (Table 3). The dog was hyponatremic (Table 3) and hypophosphatemic (Table 2). The dog had marked and dangerous hypoglycemia (Table 2). Glucose measured by instant glucose analyzer was 4.7 mmol/l after initial 5% dextrose administered to mucous membranes of mouth (Table 2).

Table 2. Laboratory findings dog 2

Parameter	Reference range	Time from the initial test

		0 h	0 h	not known	2 h	24 h
Insulin µIU/ml	8-32	101.4				
Glucose mmol/l	4.11-7.95 Instant (4-7)	1.94	4.7 (Instant)	5 (Instant)	7.57	4.74
Potassium mmol/l	3.5-5.8				3.9	
Phosphorus mmol/l	0.81-2.20	0.71			0.41	1.49
Total bilirubin µmol/l	0-15	7				7
ALT U/l	10-125	98				330
PT s	14-19	18				
aPTT s	75-105	97.3				
Thrombocytes K/µl	148-484	195				150

Note. ALT – alanine aminotransferase, PT – prothrombin time, aPTT – activated partial thromboplastin time.

Table 3 Venous blood gas results dog 2

Parameter	Reference range	Time from the initial test		
		0 h	2 h	24 h
pH	7.31-7.42	6.95	7.09	7.43
HCO3 mmol/l	20.0-29.0	9.2	16.9	18.5
PvCO2 mmHg	32.0-49.0	45.0	60.0	30.0
AnGap mmol/l				24
BE mmol/l		-22.1	-13.5	-2.7
tCO2 mmol/l	21.0-31.0	10.6	18.8	19.4
PvO2 mmHg	24.0-48.0	222.0	90.0	176.0
tHb g/dl	12.0-18.0	17.0	16.8	16.9
SvO2 %	93.0-100.0	99.0	92.0	99.0
Sodium mmol/l	144.0-160.0	140.0	142.0	153.0
Potassium mmol/l	3.5-5.8	- (error)	- (error)	4.0
Chloride mmol/l	109.0-122.0	112.0	109.0	115.0

Note. Measured blood gases in venous blood. HCO3 – bicarbonate concentration, PvCO2 – partial pressure of carbon dioxide in venous blood, AnGap – anion gap, BE – base excess, tCO2 – total concentration of carbon dioxide, PvO2- partial pressure of oxygen in venous blood, tHb – total hemoglobin, SvO2 – oxygen saturation in venous blood.

Treatment: Therapy included 5% dextrose administered to the mucous membranes of the mouth, oxygen via mask, intravenous Lactated ringer's solution with 5% dextrose, and later intravenous potassium supplementation was given to the dog. Abdominal ultrasound was done to the dog and no pregnancy was detected. The vitamin B was administered IM. After one hour, the dog's mentation was better, and it was able to swallow. The dog was fed dextrose, L-

trypthophan, heraprotein, L-glutamine and SAMe. Heart rate was 120 beats/min, respiration sounds were slightly wheezing.

Laboratory results: The reanalyzed diagnostics after two hours were blood gases, electrolytes, glucose and phosphorus. The mixed disturbance occurred as metabolic and respiratory acidosis was present as pH was 7.09 with pCO2 increased to 60.0 mmHg and bicarbonate was still under the reference (Table 3). Glucose was within reference limits (Table 2). Hypophosphatemia was more significant (Table 2).

Treatment: The dog was discharged on the same day with NAC 74 mg/kg every six hours. The dog's owners were advised to feed the dog every one to two hours. The control visit was recommended for the next day. The possible pregnancy control was recommended after two weeks.

4.2.1. The control visit

History and clinical examination: The dog was brought to the control visit on the next day after the initial treatment. No clinical signs were detected at home and the dog had a good appetite. The mental status of the dog was normal. The mucous membranes were light pink and moist, capillary refill time within reference limits. The dog's heart rate was 90 beats/min. Heartbeat synchronized with femoral pulse, metatarsal pulse was moderate. The dog's breathing frequency was slightly increased, breathing sounds were normal in auscultation. No pain was elicited in abdomen palpation. No abnormalities were detected in lymph node palpation. The dog's rectal temperature was 38.7 °C.

Laboratory results: The blood gases, plasma biochemistry (Chem 17), CBC and C-reactive protein were analyzed. The plasma ALT concentration was moderately increased as it was increased almost three times the reference (Table 2). The blood gas results revealed very small deviation from the reference limits (Table 3). The C-reactive protein was slightly increased as it was 19.1 mg/l. Complete blood count results were within reference values except basophils and MCHC slightly increased 0.11*10^9/L (reference 0.00-0.10*10^9/L) and 38.1 g/dl (reference 32.0- 37.9 g/dl) respectively. The MCV was slightly decreased 59.5 fL(reference 61.6- 73.5 fL).

Treatment: The dog was discharged on the same day with NAC 37 mg/kg every 12 hours. A control visit was recommended in one to two weeks. Frequent feeding was recommended for a few days.

4.3.Dog 3

Signalment and history: A two-year-old female dog weighting 11.2 kg was evaluated at the veterinary clinic due to ingestion of a whole package of xylitol gum. The exact package size was not known hence used estimation size for dose calculations was 80 grams. Estimated xylitol intake was from 4,857 mg/kg (method 1) to 5,495 mg/kg (method two) hence exceeding both risk limits. The general health status of the dog was good.

Clinical examination: Mentation status and behavior of the dog was apathetic but reactive. The mucous membrane color was light pink and moist with capillary refill time within reference limits. The dog's heart rate was 168 beats/min. The heartbeat synchronized with femoral pulse, metatarsal pulse was moderate, respiration rate was regular. The breathing type was costoabdominal. No abnormalities were in respiratory sounds. The sings of pain were not elicited in abdomen palpation. The lymph nodes were palpated to be symmetrical, soft and painless.

Laboratory results: The initial diagnostics included plasma biochemistry (Chem 17 clip), electrolytes, CBC and serum insulin. The serum insulin, CBC, plasma biochemistry and electrolytes were all within reference values (Table 4).

Table 4. Laboratory findings dog 3

Parameter	Reference range	Time from the initial test	
		0 h	9 days
Insulin µIU/ml	8-32	9.6	
Glucose mmol/l	4.11-7.95	5.29	5.52
Potassium mmol/l	Instant (4-7) 3.5-5.8	4.2	
Phosphorus mmol/l	0.81-2.20	1.11	1.15
Total bilirubin µmol/l	0-15	3	4
ALT U/l	10-125	43	36
Thrombocytes K/µl	148-484	150	303

Note. ALT – alanine aminotransferase.

Treatment: Therapy included induction of vomiting with apomorphine, maropitant for antiemetic treatment and intravenous Lactated ringer's solution. The vomitus contained light pink mucus and partly digested feed. The dog was fed with recovery feed. The dog was discharged on the same day with NAC 29 mg/kg PO every 12 hours. The feeding was recommended every two to four hours for one to two days. Control blood samples were recommended after one to two weeks.

4.3.1. The control visit

History and clinical examination: The dog was brought to the control visit nine days after the initial treatment. No clinical signs from xylitol toxicosis were detected.

Laboratory results: The plasma biochemistry (Chem 17) and complete blood count were analyzed. Hematology revealed slight basophilia 0.21*10^9/L (reference 0.00-0.10*10^9/L) and slightly decreased MPV 8.3 fL (8-7-13.2 fL). Plasma biochemistry results were all within reference (Table 4).

4.4. Dog 4

Signalment and history: A seven-year-old sterilized female dog weighting 21.3 kg was evaluated at veterinary clinic due to vomiting, shivering and apathy after xylitol ingestion. The owner didn't know how much the dog had eaten xylitol. The previous diagnosis of the dog was

hypothyroidism. The dog's current ongoing medication was levothyroxine 18.8 µg/kg PO every 12 hours. The dog had not been diagnosed with any allergies.

Clinical examination: The dog was shivering and not able to walk. Mucous membrane color was light pink and moist, capillary refill time within reference limits. The dog's heart rate was 84 beats/min. Heartbeat synchronized with femoral pulse, metatarsal pulse was moderate, breathing regular and costoabdominal and no abnormalities were heard in the breathing sounds. Signs of abdominal pain were not elicited. No abnormalities were noticed in palpable lymph nodes. The dog's rectal temperature was 38.5 °C.

Laboratory results: Initial diagnostics included plasma biochemistry (Chem 17 clip), blood gases, complete blood count and serum insulin. The serum insulin was within reference (Table 5). Severe hypophosphatemia was revealed (Table 5). The concentration of plasma ALT was increased more than seven times the reference (Table 5). Moderate hypokalemia was revealed (Table 6). There were not significant changes in blood gas results as pH, bicarbonate and pCO2 were all within reference values (Table 6). In CBC there were no marked changes but demonstrated slightly increased hemoglobin 21.3 g/dl (13.1-20.5 g/dl), leucopenia 3.37*10^9/L (5.05-16.76*10^9/L), neutropenia 2.49*10^9 g/dl (2.95-11.64*10^9 g/dl), lymphopenia 0.62*10^9/L (1.05-5.10*10^9/L), monocytopenia 0.14*10^9/L (0.16-1.12*10^9/L), mild thrombocytopenia 121 K/µl (148-484 K/µl), decreased platelet distribution width 9.0 fL (9.1-19.4) and plateletcrit 0.13% (0.14-0.46%).

Table 5. Laboratory findings dog 4

Parameter	Reference range	Time from the initial test		
		0	2 days	21 days
Insulin µIU/ml	8-32	8.1		
Glucose mmol/l	4.11-7.95	7.11	4.42	
Potassium mmol/l	Instant (4-7) 3.5-5.8			
Phosphorus mmol/l	0.81-2.20	0.29	1.48	
Total bilirubin µmol/l	0-15	15	5	
AST U/l	0-50			36
ALT U/l	10-125	894	641	74
Thrombocytes K/µl	148-484	121		

Note. AST – aspartate aminotransferase, ALT – alanine aminotransferase.

Table 6. Venous blood gas results dog 4

Parameter	Reference range	Time from the initial test
		0 h
pH	7.31-7.42	7.42
HCO3 mmHg	20.0-29.0	20.4
PvCO2 mmHg	32.0-49.0	34.0
AnGap – mmol/l		21
BE – mmol/l		-1.7
tCO2 mmol/l	21.0-31.0	21.4
PvO2 mmHg	24.0-48.0	227.0
tHb g/dl	12.0-18.0	19.4
SvO2 %	93.0-100.0	99.0
Sodium mmol/l	144.0-160.0	151.0
Potassium mmol/l	3.5-5.8	2.9
Chloride mmol/l	109.0-122.0	113.0

Note. Measured blood gases in venous blood. HCO3 – bicarbonate concentration, PvCO2 – partial pressure of carbon dioxide in venous blood, AnGap – anion gap, BE – base excess, tCO2 – total concentration of carbon dioxide, PvO2- partial pressure of oxygen in venous blood, tHb – total hemoglobin, SvO2 – oxygen saturation in venous blood.

Treatment: Therapy included dextrose administered PO, intravenous Lactated ringer's solution with potassium supplement. Vitamin B was administered IM. The dog was fed. The dog was discharged on the same day with NAC 30 mg/kg every 12 hours. Feeding was advised every six hours or even more often of dog wants to eat. The control visit was recommended in two days.

4.4.1. The control visit

History and clinical examination: The dog was brought to the control visit two days after the initial treatment. The clinical signs of xylitol toxicosis were not noticed but the dog had been tired on the previous day. The dog's mentation and behavior were bright, slightly anxious. Body condition score was 3/5 with normal muscle mass. The mucous membranes were light pink and moist, capillary refill time within reference limits. The dog's heart rate was 100 beats/min. The heartbeat synchronized with femoral pulse, metatarsal pulse was moderate, breathing frequency was regular and type costoabdominal, no abnormalities were heard. No pain was elicited in abdomen palpation. No abnormalities were noted in superficial lymph node palpation.

Laboratory results: The diagnostics included plasma biochemistry (Chem 17). The phosphorus was within reference values, plasma ALT enzyme concentration had started to decrease (Table 5). Lipase was also moderately over the reference as value was 2309 U/l (reference 200-1800 U/l). The dog was discharged with NAC of 30 mg/kg every 12 hours for five days. A second control visit was recommended in one to two weeks after the initial control visit.

4.4.2. The second control visit

History and clinical examination: The dog was brought to the second control visit 21 days after the initial treatment. No clinical signs of xylitol toxicosis were noticed. The dog's mentation was bright. The body condition score was 3/5 with normal muscle mass. The mucous membranes were light pink and moist, capillary refill time within reference limits. The dog's heart rate was regular, heartbeat synchronized with femoral pulse, metatarsal pulse was moderate. Breathing rate of the dog was regular, costoabdominal, breathing sounds were normal. In abdominal palpation no pain was noted, lymph nodes were normal on palpation without any pain.

Laboratory results: The diagnostics included plasma biochemistry for liver enzyme activity and kidney parameters. All results were within reference (Table 5). No further treatment for xylitol toxicosis was required.

4.5.Dog 5

Signalment and history: An eight-year-old female dog weighting 23.9 kg was evaluated at the veterinary clinic due to vomiting after the ingestion of xylitol products. Approximately two to three hours prior, the dog had ingested a little less than 90 grams of xylitol gum. Estimated ingested amount of xylitol was from 2561 mg/kg (method one) to 2897 mg/kg (method two) hence exceeding both risk limits. The dog had vomited once.

Clinical examination: The dog was bright, alert, responsive. The body condition score was 3/5 with good muscle mass. The mucous membranes were light pink and moist, capillary refill time

within reference limits. The dog's heart rate was 100 beats/min, heartbeat synchronized with femoral pulse, metatarsal pulse was moderate, breathing frequency was regular, no abnormalities in breathing type and sounds. On abdomen palpation no pain was elicited. No abnormalities were noticed on lymph node palpation.

Laboratory results: Initial diagnostics included plasma biochemistry (Chem 10 clip). The plasma concentration of ALT was moderately increased more than two times the reference (Table 7).

Table 7. Laboratory findings dog 5

Parameter	Reference range	Time from the initial test	
		0 h	12 days
Insulin µIU/ml	8-32		
Glucose mmol/l	4.11-7.95 Instant (4-7)	4.63	5.03
ALT U/l	10-125	330	128

Note. ALT – alanine aminotransferase.

Treatment: Therapy included induction of vomiting with apomorphine and maropitant for antiemetic treatment. The dog was fed with one can of moist food. The dog vomited twice, and vomitus contained a few gums. The dog was discharged on the same day with NAC 82 mg/kg PO every eight hours until control visit. Frequent feeding was advised as a small amount every four hours for next two to three days. Control visit was recommended in five to seven days.

4.5.1. The control visit

History and clinical examination: The dog was brought to the control visit 12 days after the initial treatment. The dog was more tense than on previous visit. The mucous membranes were light pink and moist, capillary refill time within reference. The dog's heart rate 120 beats/min, heartbeat synchronized with femoral pulse, metatarsal pulse was moderate. Signs of abdominal pain were not elicited. There were no noticed abnormalities on superficial lymph node palpation.

Laboratory results: Diagnostics included plasma biochemistry (Chem 10 clip). The liver value ALT had started to decrease (Table 7). The dog was discharged with NAC 54 mg/kg every 12 hours.

4.6.Dog 6

Signalment and history: A five-month-old female dog weighting 20.2 kg was brought to veterinary clinic for evaluation after ingestion of xylitol pastilles approximately one hour before. The exact product and amount were not known. The dog had tried to vomit. At home the dog was ataxic and shivering. On arrival to clinic the dog was alert.

Clinical examination: The dog was bright, alert and responsive. The BCS was 3-/5, the muscle mass was still growing. The mucous membranes were light pink and moist, capillary refill time within reference limits. The dog's heart rate was 120 beats/min, heartbeat synchronized with femoral pulse and metatarsal pulse was moderate. Breathing frequency was regular with costoabdominal type and no abnormalities were heard in breathing sounds. The dog's rectal temperature on arrival was 39.4 °C and 38.6 °C when discharged.

Laboratory results: Initially the blood glucose was measured by instant glucose analyzer and was within reference (Table 8). The other diagnostics were CBC, plasma biochemistry (chem 10 clip) and serum insulin metabolism. The plasma ALT concentration was moderately increased, and AST was more than three times the reference (Table 8). The blood glucose was slightly decreased from the laboratory reference values (Table 8). CBC revealed basophiles increased slightly 0.12*10^9 (reference 0.00-0.10*10^9), thrombocyte size as MPV slightly decreased 8.1 fL (reference 8.7-13.2 fL) (Table 8).

Table 8. Laboratory findings dog 6

Parameter	Reference range	Time from the initial test	
		0 h	<1h
Insulin µIU/ml	8-32		8.8
Glucose mmol/l	4.11-7.95 Instant (4-7)	6.0 (Instant)	4.16
Phosphorus mmol/l	0.81-2.20		1.99
Total bilirubin µmol/l	0-15		4
AST U/l	0-50		163
ALT U/l	10-125		154
Thrombocytes K/µl	148-484		235

Note. AST – aspartate aminotransferase, ALT – alanine aminotransferase.

Treatment: The dog vomited spontaneously, and no medication was administered for induction of vomiting. Therapy included vitamin B administered IM, recovery feed with addition of amino acids (L-tryptophan) and dextrose. The dog was discharged on the same day with NAC 32 mg/kg PO every 12 hours for two weeks. The control blood samples were recommended in one week.

4.7.Dog 7

Signalment and history: A four-month-old male dog weighting 5.1 kg was evaluated at the veterinary clinic due to ingestion of Läkerol-pastils a half of the package. Estimated amount of ingested pastilles was 18 grams with content of 50% xylitol. The estimated amount of ingested xylitol was from 1,765 mg/kg (method one) to 2,706 mg/kg (method two) hence exceeding both risk limits. The owner had tried to induce vomiting with salt.

Clinical examination: The mentation and behavior of the dog was bright, slightly apathetic. The mucous membranes were light pink and moist, capillary refill time within reference limits. The dog's heart rate was 144/min, the heartbeat synchronized with femoral arterial pulse rate, metatarsal pulse was moderate. The dog's breathing frequency was regular, breathing type was costoabdominal, no abnormalities were heard in the breathing sounds. On palpation the lymph nodes were symmetrical, soft and painless, no signs of pain were elicited in abdomen palpation.

Laboratory results: Initial diagnostics included plasma biochemistry (Chem 17). There was a major increase in plasma ALT concentration which was seven times the reference (Table 9). Plasma GGT was also increased moderately 7 U/L (reference 0-2 U/L).

Table 9. Laboratory findings dog 7

Parameter	Reference range	Time from the initial test
		0 h
Glucose mmol/l	4.11-7.95 Instant (4-7)	4.99
Phosphorus mmol/l	0.81-2.20	2.06
Total bilirubin µmol/l	0-15	5
ALT U/l	10-125	878

Note. ALT – alanine aminotransferase.

Treatment: Therapy included recovery feed, induction of vomiting with apomorphine, maropitant as antiemetic treatment. The dog vomited several times partly digested feed containing a light color mucus. The intravenous Lactated ringer's solution was administered.

The dog was discharged on the same day with NAC initial dose of 255 mg/kg followed by 63 mg/kg PO every six to eight hours until control visit. Frequent feeding was recommended every two to three hours for 24 hours and afterwards every four to six hours for three days. The control blood samples were recommended in five to seven days. The dog was not brought to the control visit at least to the same clinic.

4.8.Dog 8

Signalment and history: A nine-year-old female dog weighting 32 kg was evaluated at veterinary clinic due to having ingested 10 to 20 pieces of xylitol gum two to four hours prior. The estimated ingested amount of xylitol was from 523 mg/kg (method one) to 625 mg/kg (method two) hence exceeding both risk limits. The dog had vomited once. No previously diagnosed significant diseases or allergies.

Clinical examination: The mentation and behavior of the dog was bright and alert. The mucous membranes were light pink and moist, capillary refill time within reference limits. The dog's

heart rate was 100 beats/min, the heartbeat synchronized with femoral arterial pulse rate, metatarsal pulse was moderate, the dog was panting, no abnormalities were heard in the breathing sounds. On palpation the lymph nodes were symmetrical, soft and painless, on abdominal palpation no pain was detected.

Laboratory results: Initial diagnostics included plasma biochemistry (Chem 10) and serum insulin. The blood glucose was measured second time with instant glucose analyzer. The serum insulin was markedly increased (Table 10). The plasma biochemistry revealed glucose decreased slightly lower to the reference (Table 10). The ALT concentration was two times the reference (Table 10). The AST concentration was over four times the reference. The blood glucose was remeasured in two hours and it was considered as moderately increased (Table 10).

Table 10. Laboratory findings dog 8

Parameter	Reference range	Time from the initial test	
		0 h	2 h
Insulin µIU/ml	8-32	220	
Glucose mmol/l	4.11-7.95 Instant (4-7)	3.65	12.2 (Instant)
AST U/l	0-50	221	
ALT U/l	10-125	262	

Note. AST – aspartate aminotransferase, ALT – alanine aminotransferase.

Treatment: Therapy included induction of vomiting with apomorphine, maropitant as antiemetic treatment. The dog vomited moderate amount of feed with some partly digested xylitol gums. Intravenous lactated Ringer's solution was administered. The vitamin B was administered IM. The dog was fed high energy feed with tryptophan. The dog was discharged on the same day with NAC 75 mg/kg every six hours for two days followed by 75 mg/kg every 12 hours for seven days. The owner was advised to feed the dog frequently with high energy feed. The control blood samples for liver enzyme activity were recommended in two weeks.

4.9.Summary of the cases

In the case study there were more female dogs than male (Table 11). The average age was 4.6 years (Table 11). The average weight was 21.4 kg (Table 11). The clinical signs varied from the dog number five and eight that showed no clinical signs at clinic to the number two that had poor mental status and was not reacting. The most common clinical signs reported were vomiting, apathy or lethargy and shivering (Table 11).

Table 11. Signalment and recorded clinical sings (CS)

Dog (num.)	Sex (F/M)	Age (year)	Weight (kg)	CS at clinic	CS owner reported
1	M	7	22.4	Fairly alert, still able to walk	Shivering, feeble
2	F	3	35.0	Mental status poor, not reacting	Wellbeing got worse in car, peed on itself
3	F	2	11.2	Apathetic	
4	F	7	21.3	Shivering, carried into examination room	Vomiting, shivering, apathetic
5	F	8	23.9		Vomited once
6	F	0.4	20.2	Increased temp, vomited	Tried to vomit
7	M	0.3	5.1	Slightly apathetic	
8	F	9	32		Vomited once

The average quantity of xylitol gum ingested was 36.4 pieces, this also included calculation of pastilles. The estimated amount of xylitol calculated by two different methods resulted in highly similar amounts of ingested xylitol (Table 12). The estimated amounts exceeded the hypoglycemia risk limit of 100 mg/kg in all the dogs and the risk limit for liver failure 500 mg/kg in both methods (Table 12). The average ingested dose calculated by method one was 1,956.5 mg/kg and by the method two was 2,271.9 mg/kg.

Table 12. Estimated ingested amount of xylitol compared by two different methods

Dog (num.)	Estimated product intake (g) (xylitol concentration)	Estimated xylitol intake (g) Method 1	Estimated xylitol intake (mg/kg) Method 1	Estimated xylitol intake (g) Method 2	Estimated xylitol intake (mg/kg) Method 2	Estimated number of gums ingested
1	30 (95%)	28.5	1,272.3	23.1	1,030.2	23.1
2	40 (64%)	25.6	731.4	30.8	879.1	30.8
3	80 (68%)	54.4	4,857.1	61.5	5,494.5	61.5
4	Not known					
5	90 (68%)	61.2	2,560.7	69.2	2,896.7	69.2
6	Not known					
7	18 (50%)	9.0	1,764.7	13.8	2,705.9	13.8
8	26 (68%)	17.7	552.5	20.0	625.0	20.0

Notes:

Method 1. Amount of ingested xylitol estimated based on calculation of total amounts of sugar alcohols.

Method 2. Amount of ingested xylitol estimated based on each piece containing 1 gram of xylitol.

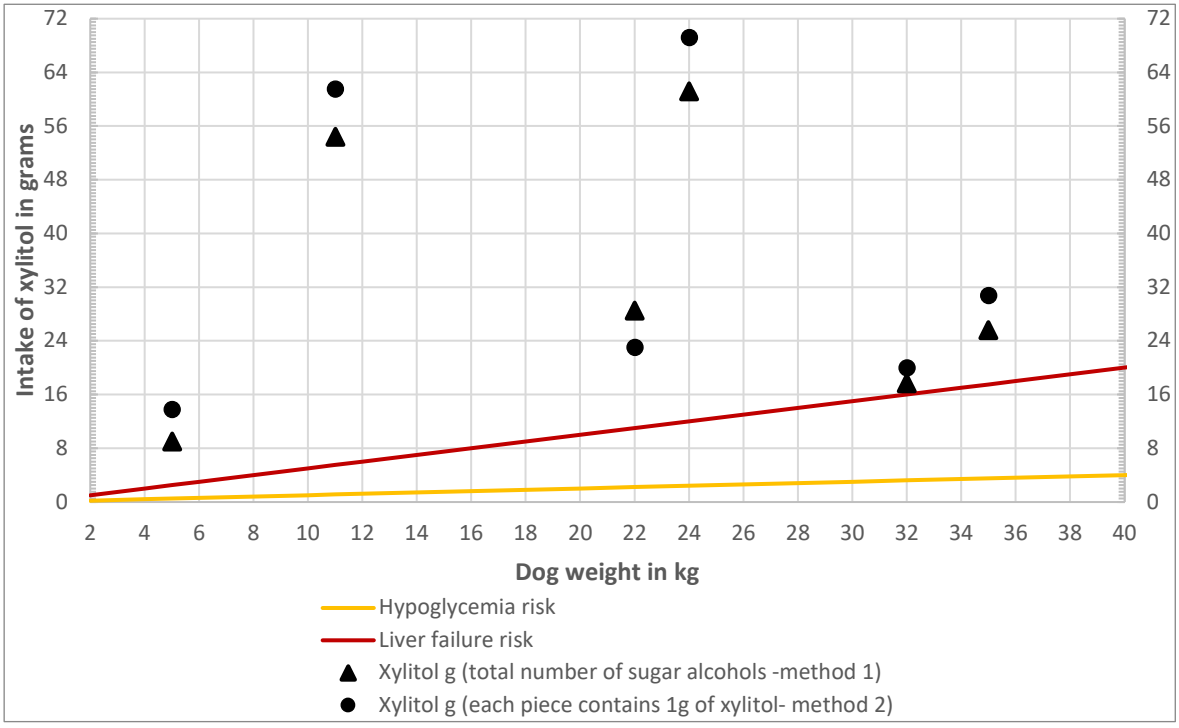

Figure 1. Hypoglycemia and liver failure risk limits as a function of dogs' weight with marked cases evaluated by two different methods.

Dogs in this study with known or estimated xylitol intake are marked, anamnesis for two dogs didn't include any estimation of the xylitol dose (Figure 1). All dogs which anamnesis

included estimate of xylitol dose, had eaten xylitol amount exceeding the value for both risk limits (Figure 1).

Table 13. Descriptive statistics of selected laboratory values

Parameter	Min Value	Average Value	Max Value	Reference Low	Reference High	Number of Tests
Insulin	8.1	64.0	220.0	8.0	32.0	6
Glucose	1.9	4.8	7.6	4.1	8.0	13
ALT	36.0	310.8	894.0	10.0	125.0	13
AST	36.0	152.5	221.0	0.0	50.0	4
aPTT	97.3	97.7	98.0	75.0	105.0	2
PT	17.8	17.9	18.0	14.0	19.0	2
Platelets	121.0	234.2	317.0	148.0	484.0	5
Total bilirubin	3.0	6.3	15.0	0.0	15.0	8
Phosphorus	0.3	1.2	2.1	0.8	2.2	9
Potassium	2.9	3.7	4.2	3.5	5.8	5

Note. ALT – alanine aminotransferase, AST – aspartate aminotransferase, aPTT – activated partial thromboplastin time, PT – prothrombin time.

The laboratory values are measured more than once for some of the dogs, hence number of tests exceed number of dogs in case study (Table 13). Serum insulin average and max values are both above upper bound of normal insulin reference values, which is to be expected (Table 13). Glucose values on the other hand are only slightly towards the lower bound. There were typically one or two glucose analyses to monitor the recovery (Table 13). Both liver cytosolic parameters ALT and AST are on average above reference limit, which is expected, max values are four to seven times higher than reference limit for both values (Table 13). The coagulation parameters aPTT and PT are only measured from two dogs, both results within reference values (Table 13). This is to be expected since none of the dogs showed signs of acute liver failure. Similarly, platelets and total bilirubin values are within reference limits, especially total bilirubin should increase in acute liver necrosis. Potassium and phosphorous can decrease due to insulin effect on cellular membranes, however no clear indication of that (Table 13).

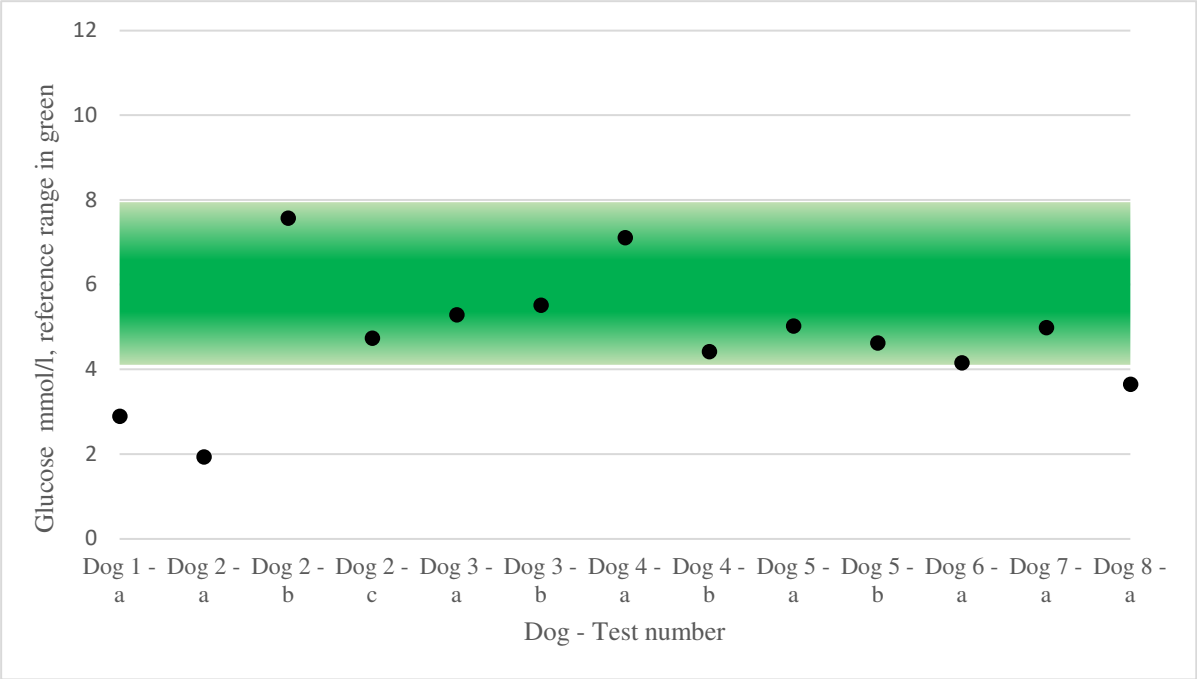

Figure 2. Glucose mmol/l in a given dog with order of tests from a to c.

In five of the dogs' blood glucose concentrations were in reference limits (Figure 2). In three of the dogs the concentration were under the lower reference and two of these dogs were considered as hypoglycemic as glucose was under 3.33 mmol/l (Figure 2). In some of the cases there is seen that initial low blood glucose (a in the figure) has been managed to correct well before the second measurement (b in the figure) and concentration increased into the reference limits (Figure 2). In some of the dogs the glucose measurements are from different days, this for example explains why dog number four blood glucose is initially higher and then lower (Figure 2). In addition, some of the dogs the blood glucose was measured only once.

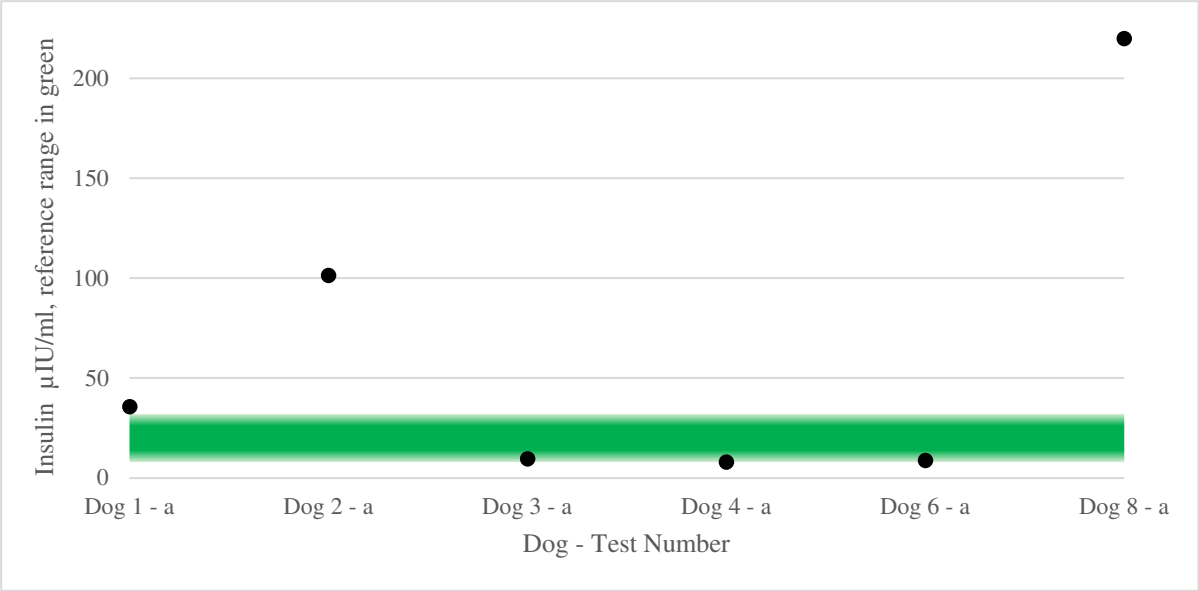

Figure 3. Insulin µIU/ml in a given dog measured once.

The serum insulin values were measured from six dogs out of eight and increased concentration were in three of the dogs (Figure 3). When compared glucose and insulin figures there can be seen that for dogs one, two and eight glucose was below the reference and these dogs had also hyperinsulinemia which would be the expectation for dog with hypoglycemia due to xylitol toxicosis (Figure 2, Figure 3).

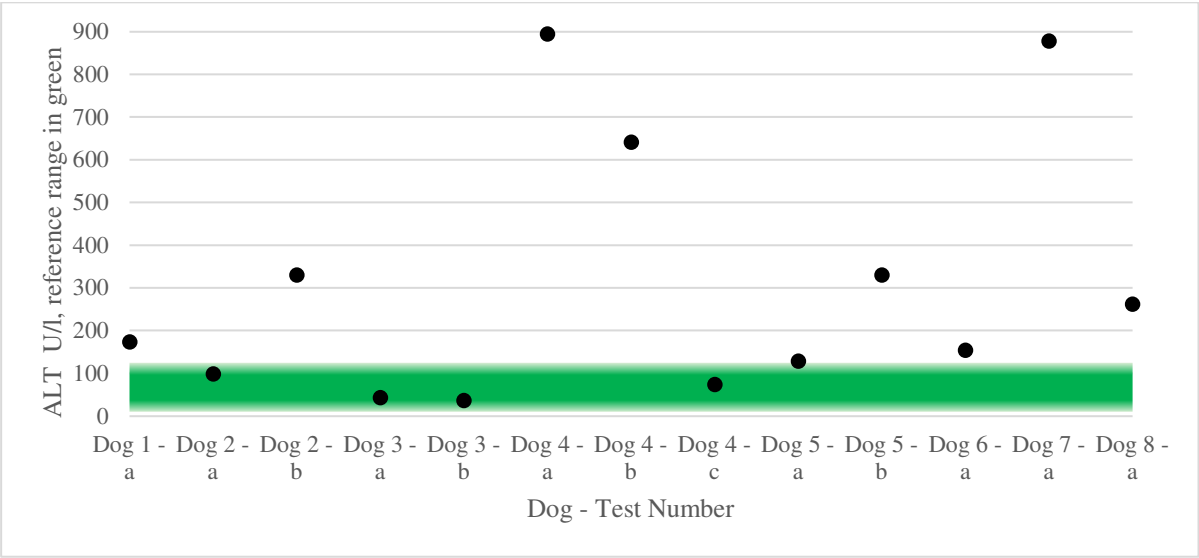

Figure 4. Alanine aminotransferase (ALT) U/l in a given dog with test order from a to c.

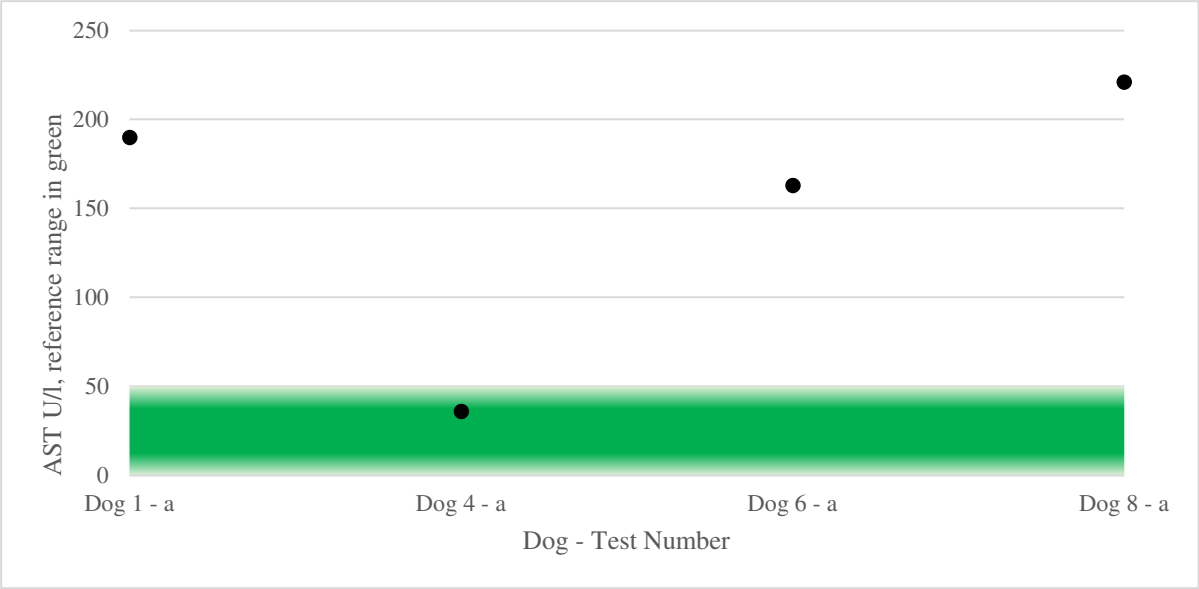

Figure 5. Aspartate aminotransferase (AST) U/l in a given dog measured once.

The increased plasma ALT concentration was measured in all the dogs except the dog number three (Figure 4). The ALT concentration was increased after the initial measurement for dogs' number two and five (Figure 4). The figure shows that highest ALT concentration was measured from dogs' number four and seven. The control sample results show that for dog number four the ALT values decreased to the reference range during the treatment period of three weeks (Figure 4). The plasma AST concentration was measured only from four dogs and in three of them it was increased from the reference (Figure 5).

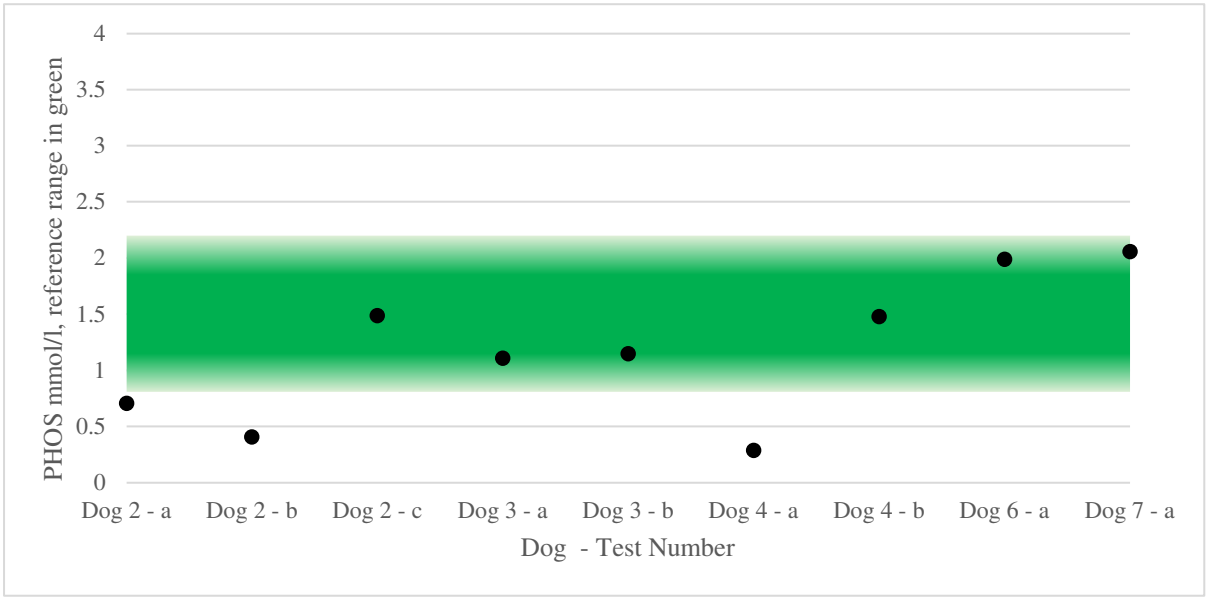

Figure 6. Phosphorus (PHOS) mmol/l in a given dog with order of test from a to c.

Three of the dogs had plasma phosphorus concentration under 0.81 mmol/l indicating hypophosphatemia (Figure 6). For the other dogs the phosphorus was within the reference range (Figure 6).

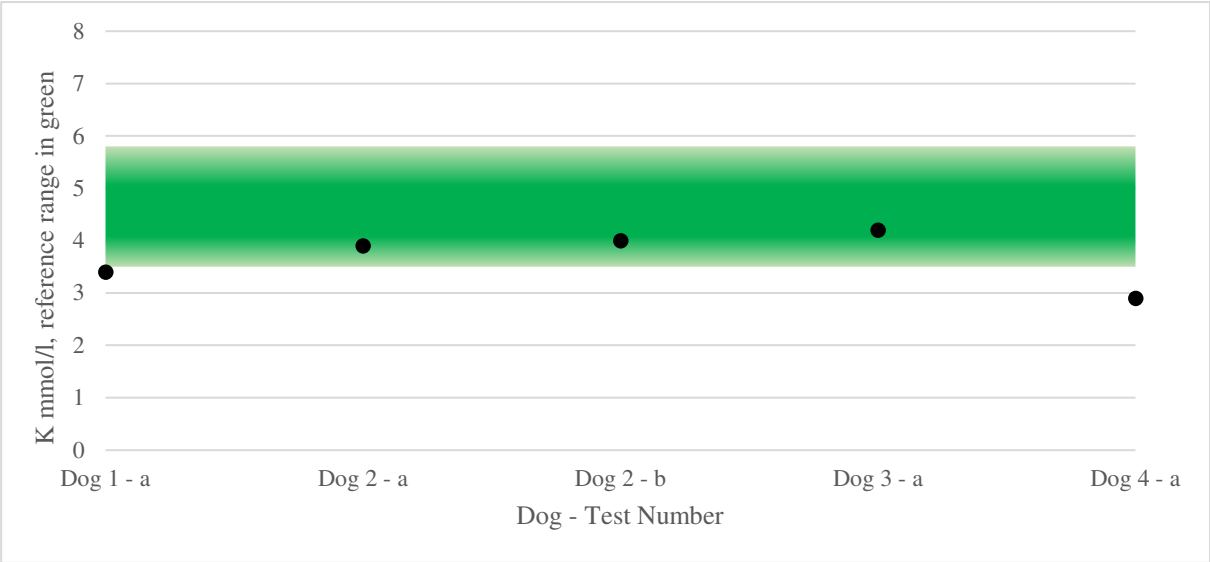

Figure 7. Potassium (K) mmol/l in a given dog with order of test from a to b.

The plasma potassium values were measured from four of the dogs in which two of the dogs had potassium concentration under the reference (Figure 7). The dog number one first measurement was slightly under the reference as potassium was 3.4 mmol/l whereas the dog number four had moderate hypokalemia as potassium was 2.9 mmol/l as dangerous hypokalemia is considered when potassium is less than 2.5 mmol/l (Figure 7).

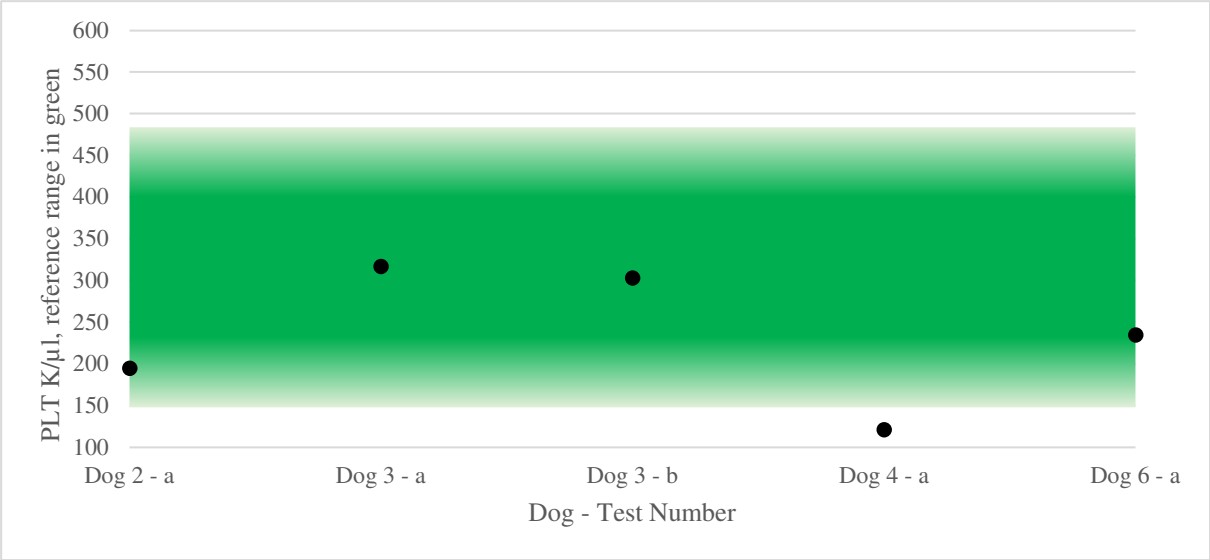

Figure 8. Platelets (PLT) K/µl in a given dog with order of test from a to b.

The platelet values were measured only in four dogs (Figure 8). Only in one dog thrombocytopenia occurred (Figure 8).

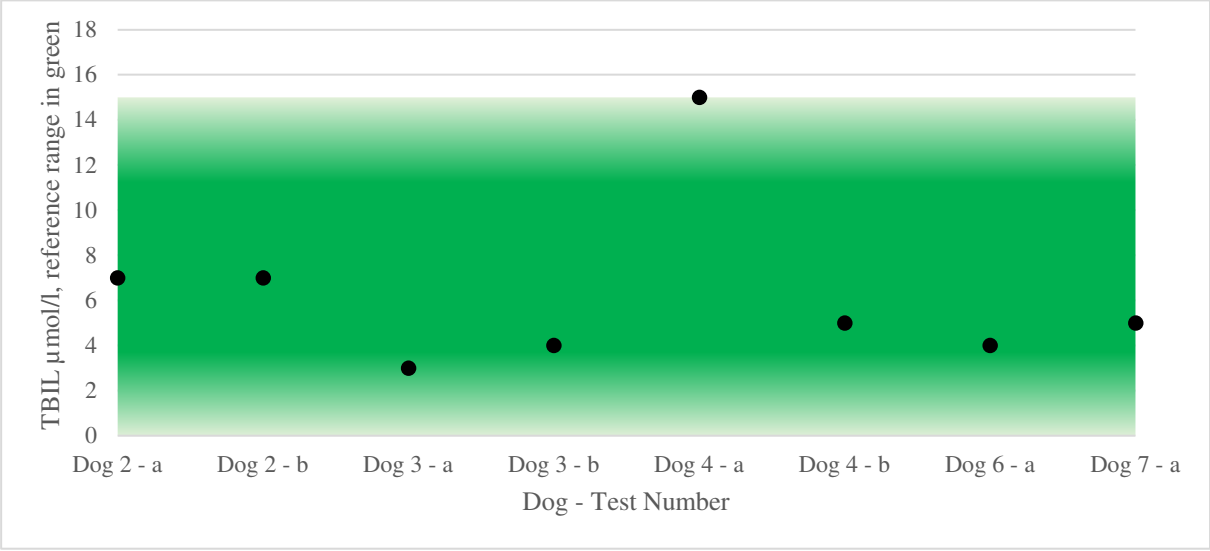

Figure 9. Total bilirubin (TBIL) µmol/l in a given dog with order of test from a to b.

Total plasma bilirubin values were measured in five of the dogs (Figure 9). Only for one of the dogs the bilirubin was increased slightly from the reference limit 15 µmol/l (Figure 9).

Medically induced vomiting was generated in five of the eight dogs with apomorphine and later given antiemetic treatment with maropitant. Dogs number four, five and six vomited spontaneously (Table 11). Therefore, no induction of vomiting was given to dog number four

and six, but vomiting was induced in dog number five. The mentation status of the dog number two was poor hence no vomiting was induced. Six of the eight dogs received intravenous treatment with Lactated ringer's solution and dog number two received in addition intravenous dextrose solution and potassium and dog number four also received intravenous potassium. Feeding was given to seven out of eight dogs also including dog number two who was fed when it was able to swallow. The amino acid l-tryptophan in addition to dextrose were most commonly given with feed. The l-tryptophan was given to four of the dogs and PO additional dextrose to three of the dogs. In addition, the dog number two was fed with heraprotein, l-glutamine and SAMe. The five of the dogs were given intramuscular vitamin B. All the owners were advised to give NAC at home in addition of frequent feeding.

5. DISCUSSION

The most common clinical signs associated with xylitol toxicosis are vomiting, lethargy, diarrhea, ataxia, seizures, restlessness and anorexia (Duhadway *et al.,* 2015). The clinical signs detected in our case study were typical of xylitol toxicosis as most common clinical signs reported were vomiting, apathy or lethargy and shivering (Table 11). In the study of Xia *et al.* (2009) most of the dogs became depressed and inactive, one dog had dystataxia and mild tremors and some dogs vomited within 0.5-1 hour after dosing of xylitol.

Absorption of xylitol can reach peak plasma concentrations in only 30 minutes (Murphy and Dunayer, 2018). The time is limited for seeking veterinary treatment and effective decontamination before clinical signs or total absorption of xylitol occurs. There are different recommendations for how long emesis can still be effective after ingestion of xylitol. Absorption speed could be impacted by the structure of the product ingested and amount of mastication (Murphy and Dunayer, 2018). In addition, possible wrapper materials can affect absorption time. The important aspect on decontamination is occurrence of clinical signs. If clinical signs occur or the dog has already vomited induction of emesis should not be done (Murphy and Dunayer, 2018).

To find out the amount of the ingested xylitol dose and the time that had passed from the ingestion to the treatment proved to be challenges of the case study. The estimation was mainly based on the dog owner's evaluation of the ingested xylitol amount and there is a possibility for high variance in dose. The time passed from ingestion to the patient evaluation at the veterinary clinic was not mentioned in the clinic patient database in four of the treated dogs. The time passed from ingestion to evaluation at veterinary clinic varied from one hour (in three of the dogs) to two to four hours in one dog.

In the study methods one and two were used for estimating the dose of ingested xylitol. Most of the time, the simple approach of the method two led to slightly higher estimated doses, which is preferable since it is safer to overestimate the dose (Figure 1). However, the exact ingested amount of xylitol is difficult to evaluate. The estimation can be varied based on the owner's

evaluation of ingested amount, size of the package and exact product name. The estimations based on both methods in the study show that all the patients brought to the clinic, exceeded both hypoglycemia and liver failure risk limits (Figure 1).

The possibility for hypoglycemia to develop was expected in the study. In the case series five of the dogs' blood glucose concentration were in reference range. The values were under the lower reference in three of the dogs and two of these were considered hypoglycemic (Figure 2). Hypoglycemia occurred in the 15.6% of xylitol ingested dogs some time during hospitalization in the study of Duhadway et *al*. (2015). Hypoglycemia might develop within 30-60 minutes after xylitol ingestion (Dunayer, 2004) but can be delayed up to 12 hours (Dunayer, 2006). There can be possibility that the blood glucose values were measured in some dogs at a time when glucose had started to increase. The other possibility is delayed hypoglycemia in some of the dogs. In the experimental study of Xia *et al.* (2009) blood glucose started to decrease 30 minutes after the xylitol dose and was significantly lower than the control group at 50-60 minutes. The blood glucose started to increase to similar concentrations as in the control group at 90 minutes (Xia *et al.,* 2009). This supports the possibility that in some dogs the blood glucose can already be increased as the exact time for ingestion is not known in the case study. In the study one dog had hypoglycemia, cortisol and ACTH values markedly increased. This can be due to counter-regulatory hormones (Idowu and Heading, 2018), hyperadrenocorticism or stress (Nelson, 2012). Hyperinsulinemia can also increase ACTH concentration (Nelson, 2012). In general, when considering xylitol ingestion hypoglycemia is not the most detected laboratory value change as was detected in our study and in the broader study population of Duhadway et *al*. (2015).

The serum insulin concentrations have been rarely measured in case reports or retrospective case studies previously. In the study insulin values were measured from six dogs and increased values were in three dogs (Figure 3). In dogs ingestion of xylitol results in dose dependent increase in plasma insulin concentration (Duhadway *et al*., 2015). Therefore, the hyperinsulinemia was expected to be detected in the case study. However, hyperinsulinemia was detected in only half of cases where serum insulin concentration was measured (Figure 3). In the study of Xia *et al*. (2009) the dogs were orally dosed 1,000-4,000 mg of xylitol/kg. The dogs were reported to show sharp increase of plasma insulin concentration within 20 minutes with peak at 40 minutes after ingestion (Xia *et al*., 2009). Weakness in our case study was that

the time of xylitol ingestion was not known precisely. When glucose and insulin measurements were compared it was detected that for dogs one, two and eight glucose was below and insulin above the reference values. This would be the typically expected for a dog with hypoglycemia due to xylitol ingestion.

In addition, one problem in the case series was that the half-life of insulin is typically short. Therefore, the serum insulin concentrations can be already decreased to the reference limits. In the study of Earnhardt *et al.* (2002) the half-life in healthy dog's plasma insulin curve was derived for fast and slow component half-lives. The 89% of insulin clearance occurred at fast component. The grand means for fast and slow component insulin half-lives were 2.7 ± 0.1 minutes and 42 ± 5.3 minutes respectively (Earnhardt el al., 2002). However, this study was done with healthy dogs without xylitol ingestion. The half-life of insulin can vary greatly with xylitol toxicosis compared to a healthy dog's endogenous insulin half-life. In the study of Xia *et al*. (2009) dogs were orally administered aqueous xylitol and insulin values were still increased at 180 minutes compared to the control group. Another reason for the insulin within reference range can be the difference of the real dose ingested and the calculated estimated dose of xylitol. Therefore, insulin concentrations should not lead to diagnosis of xylitol toxicosis alone when ingestion of xylitol is not certain and other differentials should be considered.

The liver enzyme concentrations can be increased in xylitol toxicosis. The most common biochemical abnormality was increased ALT and/or total bilirubin in the study of Duhadway *et al*. (2015). Most of dogs had mild increase in ALT but four of the dogs had increased ALT for more than 800 U/l (Duhadway *et al*., 2015). In the study of Xia et al. (2009) plasma ALT and AST activities increased dose dependently after xylitol administration. The ALT concentration increased from three to tenfold from low to high dose group respectively compared to control value. The plasma AST concentration increased from 2.5 to ninefold respectively (Xia et al., 2009).

The plasma ALT concentration was increased in seven of the eight dogs and increased AST concentration was in three out of four measured values. The increased plasma concentration of AST and ALT were most commonly changing laboratory value detected in the study. The difference to the study of Duhadway *et al*. (2015) was that in our study only one of the dogs had mild increase in ALT and in other dogs ALT was markedly increased (Figure 4). This

difference in our study can be due to higher doses of ingested xylitol. The average estimated ingested dose was 1,957 mg/kg and 2,272 mg/kg evaluated by method one and two respectively. Whereas in the study of Duhadway *et al*. (2015) the mean ingested xylitol dose was 320 mg/kg. No significant difference was detected between estimated xylitol dose in dogs with increase in ALT and/or total bilirubin concentrations and those with ALT and total bilirubin within reference in the study of Duhadway *et al*. (2015). In contrast in the study of Xia *et al.* (2009) the ALT and AST concentrations increased dose dependently. This can be due to the retrospective study as the exact amount of ingested xylitol is not known precisely as compared to controlled experimental study.

In the case series the plasma ALT concentration was increased after the initial measurement in two of the dogs and this can be due to delayed hepatopathy (Figure 4). Hepatopathy can develop in one to two hours post ingestion but delayed onset is possible with 9-72 hours post ingestion (Peterson, 2013). In the study of Xia *et al.* (2009) the highest concentration of ALT was four to eight hours after dosing of xylitol. There is a possibility that in our study the highest concentration of ALT was not measured. The highest ALT concentration in the study was measured from the dog number four and seven. The control blood sample results show that in dog number four the ALT values decreased to reference range during the treatment period of three weeks (Figure 4).

In three dog's plasma AST concentration was increased with 3.3fold to 4.4fold (Figure 5). This can be assumed as in the study of Xia *et al.* (2009) the AST values increased to highest level within first four hours from ingestion. Even though AST is not as liver specific as ALT it can be assumed that significant increase in AST when occurring at the same time of significant increase in ALT can be due to hepatocellular damage (Willard and Twedt, 2012). However, the dog number one, six and eight with increased AST concentration did not show significant increase in ALT. Significant increase in both ALT and AST concentration would suggest more serious hepatocellular damage as ALT is released from cytosolic damage and AST in mitochondrial damage of hepatocytes (Willard and Twedt, 2012).

Total bilirubin was increased slightly from the reference in one of five dogs (Figure 9). Increased plasma total bilirubin was also detected in the study of Xia *et al.* (2009) and was thought to be due to hemolysis. It is known when glucose supply is markedly reduced,

erythrocyte membranes are ruptured and hemoglobin is released and degraded to bilirubin Xia *et al.* (2009).

In our study the platelet count was measured in four dogs and one had mild thrombocytopenia (Figure 8). The dog didn't show signs of acute liver failure or DIC. Hence mild thrombocytopenia can be due to platelet clumping because no manual counting was done in addition. Other cause for decreased platelet count can be hypothyroidism. The dog was earlier diagnosed with hypothyroidism. Hypothyroidism is associated with general bone marrow depression causing mild thrombocytopenia which is not clinically significant (Brooks, 2017). Generally, the causes of thrombocytopenia can be separated into production defects, destruction and consumption defects and dilution defects (Brooks, 2017).

The decreased plasma concentration of phosphorus and potassium was expected in the study. Hypophosphatemia occurred in two out of five dogs of which plasma phosphorus concentration was measured (Figure 6). The plasma potassium concentration was measured from four of the dogs. The plasma potassium concentration of one dog was slightly under the reference whereas another had moderate hypokalemia (Figure 7). These changes in potassium and phosphorus can be caused due to insulin effect on cell membranes. Insulin can shift potassium and phosphorus intracellularly producing low laboratory values. For example, the dog number one had hypoglycemia, hypophosphatemia and slightly decreased potassium from the reference values. The dog number two had hypoglycemia, hypophosphatemia but measured potassium was within the reference values. This can be due to reason that initial potassium values were not known and only after the initiation of the treatment the results were available. In the study of Xia *et al.* (2009) the plasma potassium and inorganic phosphorus concentrations were dose-dependently decreased. The plasma potassium and inorganic phosphorus values remained lower than in the control group and predose values of xylitol for three hours (Xia *et al.,* 2009). In contrast in the study of Duhadway *et al.* (2015) the second most common serum biochemistry abnormality after increased liver values was hyperphosphatemia followed by hypophosphatemia. However, six of seven dogs that were hyperphosphatemic were 12 months or less (Duhadway *et al*., 2015). Hyperphosphatemia in these cases can be due to developing bone (Duhadway *et al*., 2015, Nelson, 2012). In addition, three dogs were hypophosphatemic and all three were also hypoglycemic on presentation (Duhadway *et al.,* 2015).

In our study generally, the dogs were treated as recommended in the literature. The main differences in the treatment protocol to the literature were dextrose administration route and duration of the treatment at the clinic. Therefore, glucose reevaluation was not possible every two hours for 12 hours and re-evaluation of electrolytes was mostly not possible in eight to 12 hours. This is important aspect when considering that in some of the xylitol ingestion cases there is no possibility to hospitalize the dog for the next 12-24 hours for different reasons and the outcome of the treatment might still be successful.

The main differences in the treatment protocol to the literature were that most of the dogs received dextrose PO instead of IV. Only one of the dogs received IV dextrose. PO feeding was administered to seven dogs including the one that received previously dextrose IV. It has been demonstrated in the earlier studies in humans and dogs that when presented with moderate oral glucose load the liver extracts one third of the glucose while muscles and fat one third and non-insulin-sensitive tissues dispose remaining (Moore et al., 2012). It has also been demonstrated that entry of glucose into the portal vein stimulated net hepatic glucose uptake and hepatic glycogen synthesis significantly greater than when glucose was delivered via peripheral vein. Thus the portal vein signal was responsible for enhancement of net hepatic glucose uptake during oral, enteral or portal vein glucose delivery (Moore et al., 2012). The portal glucose signal was also associated with suppression of muscle glucose uptake with increase of liver glucose uptake. In addition when the insulin concentration and hepatic glucose load were kept constant, the net hepatic glucose uptake was approximately 2-fold greater when glucose was delivered via the portal versus peripheral vein (Moore et al., 2012).

The importance of PO glucose delivery could be essential in xylitol toxicosis as one mechanism is thought to be associated with hepatopathy is depletion of liver ATP -stores. It should be noted that PO glucose delivery is possible only for dogs that are stable, and no contraindications occur. This suggests that dogs with dangerous clinical signs and hypoglycemia should be treated first with intravenous glucose. After the dogs are stable, and no contraindications occur the PO glucose can be added to treatment protocol.

Liver supplementation products were broadly used in the case study as amino acid l-tryptophan was administered to four dogs with feed. In addition, the dog number two received PO heraprotein, l-glutamine and SAMe. All of the owners were advised to give NAC at home in

addition of frequent feeding. The dose used for NAC varied from 232 to 255 mg/kg (initial dose) and 29 mg/kg to 82 mg/kg (followed dosages) therefore generally lower than recommended in the literature. Two of the dogs received initial high dose of NAC. In general, the treatment success was good especially when considering the average dose ingested that was high compared to some other case reports. No dog had indications for liver failure in our study.

In our study four of the treated dogs were brought for the control visit. The dog number two was brought for control visit on the next day and the dog number four was brought for the control visit on the second day after the xylitol ingestion. The dog number five was brought to control visit after five days and the dog number three was brought to control visit after nine days. The control visit showed in dog number two that ALT had increased slightly from the previous measurement whereas phosphorus had increased to the reference limits by the control visit (Figure 4, Figure 6). The dog number four ALT concentration had decreased to the reference by the second control visit 21 days from the xylitol ingestion and phosphorus was in the reference at the first control visit (Figure 4). The dog number five ALT concentration had slightly increased by the control visit (Figure 4). Due to the lack of control visits in our study in all the treated dogs the total recovery is difficult to evaluate, only the dog number four control blood sample results show that liver values were decreased to the reference limits.

Overall, it is impossible to evaluate treatment effectiveness because there are not enough control appointments to evaluate the recovery in this retrospective case study and due to limited sample size, these results are only valid in the case study sample.

Xylitol toxicosis treatment is generally of long duration, even if there is not clinical signs or laboratory changes. Duration of treatment should be long due to the possibility of delayed onset of clinical signs and for these reason's hospitalization should last ideally 12-24 hours (Dunayer, 2004; 2006). In addition hepatic enzyme reevaluation should be done due to possibility for delayed hepatopathy at 9-72 hours post ingestion (Peterson, 2013). All dogs that are suspected or known to have ingested xylitol should be monitored preferably for several hours and treated accordingly also taken into account the need of preventative treatment of liver toxicosis with supportive products for liver function.

6. CONCLUSIONS

The current recommendation for a treatment protocol is clear and movement of patient from a clinic to a veterinary hospital may not be needed if there is enough time for the treatment and patient condition including serial blood parameters can be followed. However, this does not include the patients with serious clinical signs or indications for liver failure. When patient is sent home earlier than 12-24 hours the importance of home monitoring and frequent feeding cannot be underlined enough.

The main findings of the case study were that ingested xylitol dose was high exceeding both risk limits. The main differences to the recommended treatment protocol in the literature were dextrose administration route and duration of initial treatment at the clinic. The dextrose solution was generally administered PO instead of IV in the case material. The initial duration of the treatment at the clinic was less than recommended 12-24 hours.

In our study none of the dogs developed acute liver failure. The patients that were brought to clinic for all the control visits it was seen that liver enzymes decreased back to the reference limits during the treatment period. Therefore, the treatment was successful. This study suggests that management of xylitol toxicosis could also be possible by PO glucose instead of intravenous glucose when patient is generally well, and no hypoglycemia occurs. However due to lack of the control visits for some dogs the general evaluation of the treatment success was not possible. The main finding in the laboratory values was that increase in ALT and AST enzyme activity were most common and consistent with the literature. Therefore, this thesis further supports ALT and AST liver cytosolic parameters being useful markers for the xylitol ingestion when ingested dose exceeds both risk limits.

In xylitol toxicosis research there are important ethical aspects to consider. As xylitol is proven toxicant for dogs, it would not be ethical to conduct controlled clinical studies. However more larger scale case studies could be made where dogs have accidentally ingested xylitol. Since xylitol toxicosis is common in Finland there should be more data available for further studies of xylitol toxicity and treatment protocol.

REFERENCES

Brooks, M. B. (2017). Thrombocytopenia, thrombocytosis. In: S. J. Ettinger., E. C. Feldman., E. Cote. eds. Textbook of veterinary internal medicine, 8th ed. Elsevier. pp. 758-762.

Cocco, F., Carta, G., Cagetti, M. G., Strohmenger, L., Lingström, P. and Campus, G. (2017). The caries preventive effect of 1-year use of low-dose xylitol chewing gum. A randomized placebo-controlled clinical trial in high-caries-risk adults. *Clinical Oral Investigations*, 21, pp. 2733–2740.

Cope, R. (2004). A screening study of xylitol binding in vitro to activated charcoal. *Veterinary and Human Toxicology*, 46, pp. 336–337.

Cortinovis, C. and Caloni, F. (2016). Household food items toxic to dogs and cats. *Frontiers in Veterinary Science,* 3, 26.

Duhadway, M. R., Sharp, C. R., Meyers, K. E. and Koenigshof, A. M. (2015). Retrospective evaluation of xylitol ingestion in dogs: 192 cases (2007-2012). *Journal of Veterinary Emergency and Critical Care,* 25, pp. 646–654.

Dunayer, E. K. (2004). Hypoglycemia following canine ingestion of xylitol-containing gum. *Veterinary and Human Toxicology,* 46, pp. 87–88.

Dunayer, E. K. (2006). New findings on the effects of xylitol ingestion in dogs. *Veterinary Medicine*, 101, pp. 791–798.

Dunayer, E. K. and Gwaltney-Brant, S. M. (2006). Acute hepatic failure and coagulopathy associated with xylitol ingestion in eight dogs. *Journal of the American Veterinary Medical Association*, 229, pp. 1113–1117.

Earnhardt, R. C., Veldhuis, J. D., Cornett, G. and Hanks, J.B. (2002). Pathophysiology of hyperinsulinemia following pancreas transplantation: altered pulsatile versus basal insulin secretion and the role of specific transplant anatomy in dogs. *Annals of Surgery*, 236, pp. 480-491.

Fracassi, F. (2017). Canine diabetes mellitus. In: S. J. Ettinger., E. C. Feldman., E. Cote. eds. Textbook of veterinary internal medicine, 8th ed. Elsevier. p. 4299.

Gonzalez, A. L. and Silverstein, D. C. (2019). Hypoglycemia. In: K. J. Drobatz., K. Hopper., E. Rozanski., D. C., Silverstein. eds. Textbook of small animal emergency medicine, 1st ed. John Wiley & Sons, Inc., pp. 719–725.

Idowu, O. and Heading, K. (2018). Review article compte rendu hypoglycemia in dogs: Causes, management, and diagnosis. *Canadian Veterinary Journal*, 59, pp. 642–649.

Janket, S. J., Benwait, J., Isaac, P., Ackerson, L. K. and Meurman, J. H. (2019). Oral and systemic effects of xylitol consumption. *Caries Research*, 53, pp. 491–501.

Jerzsele, Karancsi, Z., Pászti-Gere, E., Sterczer, Bersényi, A., Fodor, K., Szabó, D. and Vajdovich, P. (2018). Effects of p.o. administered xylitol in cats. *Journal of Veterinary Pharmacology and Therapeutics*, 41, pp. 409–414.

Laitala, M.-L. and Pienihäkkinen, K. (2020) Säännöllisen ksylitolipurukumin tai -pastillin käytön vaikutus hampaiden reikiintymiseen ja karieksen varhaisvaiheiden syntyyn ja etenemiseen. Current Care Guidelines, The Finnish Medical Society Duodecim, https://www.kaypahoito.fi/nak06746, 22.11.2020.

Lidbury, J. A. (2017).General principles in the treatment of liver disease. In: Ettinger, S. J., Feldman, E. C., Cote, E. eds. Textbook of veterinary internal medicine, 8th ed. Elsevier. pp. 1621–1623.

Lowe, C. and Anthony, J. (2020). Pilot study of the effectiveness of a xylitol-based drinking water additive to reduce plaque and calculus accumulation in dogs. *Canadian Veterinary Journal,* 61, pp. 63–68.

Ly, K. A., Milgrom, P. and Rothen, M. (2008). The potential of dental-protective chewing gum in oral health interventions. *The Journal of the American Dental Association*, 139, pp. 553–563.

Mäkinen, K. K. (2015). Ksylitoli - nimi on ongelma? In: Mäkinen, K. K., editor. Sen täytyi tapahtua - Mitä jokaisen suomalaisen tulisi tietää ksylitolista. Mediapinta Oy. p 33.

Mäkinen, K. K. (2016). Gastrointestinal disturbances associated with the consumption of sugar alcohols with special consideration of xylitol: Scientific review and instructions for dentists and other health-care professionals. *International Journal of Dentistry*, 2016, pp. 1-16.

Moore, M.C., Coate, K. C., Winnick, J. J., An, Z. and Cherrington, A. D. (2012). Regulation of hepatic glucose uptake and storage in vivo. *Advances in Nutrition*, 3, pp. 286-294.

Murphy, L. A. and Dunayer, E. K. (2018). Xylitol toxicosis in dogs: An update. V*eterinary Clinics of North America - Small Animal Practice*, 48, pp. 985–990.

Nelson, R. W. (2012). Endocrine, metabolic and lipid disorders. In: M. D. Willard. and H. Tvedten.eds. Small animal clinical diagnosis by laboratory methods, 5 th ed. W.B. Saunders. pp. 161-182.

Newton, J. T., Awojobi, O., Nasseripour, M., Warburton, F., Di Giorgio, S., Gallagher, J. E. and Banerjee, A. (2019). A systematic review and meta-analysis of the role of sugar-free chewing gum in dental caries. *Journal of Dental Research, Clinical & Translational Research*, 5, pp. 214–223.

Peterson, M. E. (2013). Xylitol. *Topics in Companion Animal Medicine*, 28, pp. 18–20.

Plumb, D. C. (2018). Plumb's Veterinary Drug Handbook 9 th edition, 9th ed. PharmaVet Inc. pp. 13-1213.

Rahman, A., Islam, S., Rahman, M. A. and Islam, M. S. (2014). Xylitol improves pancreatic islets morphology to ameliorate type 2 diabetes in rats: A dose response study. *Journal of Food Science,* 79, pp. 1436–1442.

Schmid, R. D. and Hovda, L. R. (2016). Acute hepatic failure in a dog after xylitol ingestion. *Journal of Medical Toxicology*, 12, pp. 201–205.

Shakil A, O. (2005). Predicting the outcome of fulminant hepatic failure. *Liver Transplantation*, 11, pp. 1028–1030.

Suokko, M., Saloranta, L., Lamminen, T., Laine, T. and Elliott, J. (2020). Ropinirole eye drops induce vomiting effectively in dogs: A randomised, double-blind, placebo-controlled clinical study. *Veterinary Record*, 186, 283.

Tapiainen, T., Kontiokari, T., Sammalkivi, L., Ikähiemo, I., Koskela, M. and Uhari, M. (2001). Effect of xylitol on growth of Streptococcus pneumoniae in the presence of fructose and sorbitol. *Antimicrobial Agents and Chemotherapy*, 45, pp. 166–169.

Ur-Rehman, S., Mushtaq, Z., Zahoor, T., Jamil, A., Murtaza, M. A. (2015). Xylitol: A review on bioproduction, application, health benefits, and related safety issues. *Critical Reviews in Food Science and Nutrition*, 55, pp. 1514–1528.

Wang, Y. M. and van Eys, J. (1981). Nutritional significance of fructose and sugar alcohols. *Annual Review of Nutrition,* 1, pp. 437–475.

WHO. (1977). Summary of toxicological data of certain food additives: WHO food additives series no. 12: xylitol. International Programme on Chemical Safety, World Health Organization, http://www.inchem.org/documents/jecfa/jecmono/v12je22.htm, 16.11.2020.

Willard, M, D. and Twedt, H. (2012). Gastrointestinal, pancreatic and hepatic disorders. In: M. D. Willard., H. Tvedten. eds. Small animal clinical diagnosis by laboratory methods. 5th edn. W.B. Saunders. pp. 215-216.

Woods, H. F. and Krebs, H. A. (1965). Xylitol metabolism in the isolated perfused rat liver. *Annals of the New York Academy of Sciences*, 119, pp. 1013–1028.

Xia, Z., He, Y. and Yu, J. (2009). Experimental acute toxicity of xylitol in dogs. *Journal of Veterinary Pharmacology and Therapeutics*, 32, pp. 465–469.

Zhang, L. W.,Koci, J., Jeffery, B., Riviere, J. E. and Monteiro-Riviere, N. A. (2015). Safety assessment of potential food ingredients in canine hepatocytes. *Food and Chemical Toxicology*, 78, pp. 105-115.

APPENDIXES

Appendix 5. Non-exclusive licence for depositing the final thesis and opening it for the public and the supervisor's (supervisors') confirmation for allowing the thesis for the defence

Hereby I, Julia Eeva-Maria Sulonen (09/02/91)

1. grant Eesti Maaülikool, the Estonian University of Life Sciences, a free-of-charge non-exclusive licence to store the final thesis titled Xylitol toxicosis in dogs: case series study supervised by Kristel Peetsalu, Toomas Orro for

   1.1. preservation;
   1.2. depositing a digital copy of the thesis in the archive of DSpace and
   1.3. opening it for the public on the Web

   until the validity of the term of protection of copyright.

2. I am aware that the author retains the same rights as listed in point 1;

3. I confirm that by being issued the CC licence no rights deriving from the Personal Data Protection Act and the Intellectual Property Rights Act have been infringed.

Author of the final thesis _____ signature

In Helsinki, 10.05.2021

The core supervisor's approval for the final thesis to be allowed for defence

This is to confirm that the final thesis is allowed for defence.

....
Supervisor's name and signature Date

....
Supervisor's name and signature Date

6